PSYCHONEUROENDOCRINE AND SYMPATHETIC STRESS RESPONSE IN HIV INFECTED PATIENTS UNDER HAART AFTER COGNITIVE BEHAVIOURAL STRESS MANAGEMENT TRAINING

Dissertation
presented to the Faculty of Arts
of
the University of Zürich
for the degree of Doctor of Philosophy

by
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accepted in recommendation of
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University of Zürich
2007

Acknowledgements

The completion of this dissertation was made possible through the support and cooperation of many persons.

First, I would like to thank Prof. Dr. U. Ehlert for her practical and scientific supervision and continuous support for the study.

Special thanks got to Dr. J. Gaab, who provided thoughtful guidance and supervision during my research. I am grateful for all his support!

My thanks also go to the members and patients of the SHCS, especially to Dr. R. Weber, Dr. B. Ledergerber and Christina Grube for the successful cooperation, making it possible to perform this multicentre study.

Thanks also to my colleagues and friends especially Vroni, Ulli and Aliki and to our student team and I thank David to proofreading my text.

Many thanks to my parents for encouraging me and giving me strength during every part of my life. Most importantly I thank Andreas for his love and his confidence in me.

Abstract

Background: Stress has an important impact on disease progression in HIV infected patients. Dysregulations of the hypothalamic pituitary adrenal (HPA) axis and the sympathetic nervous system (SAMS) were discussed as potential mediating mechanisms between stress and health outcome. Previous studies demonstrated that cognitive behavioural stress management (CBSM) training alters stress parameters in HIV patients. However the influence of CBSM on stress outcomes was never evaluated under stress conditions and findings only referred to HIV infected populations in the pre-HAART (highly active antiretroviral therapy) era. Therefore we evaluated the efficacy of CBSM training on the HPA axis and on the SAMS in HIV infected patients undergoing HAART with the intention to identify possible alterations in stress reactivity.

Method: In a multicentre study we randomly assigned HIV infected men and woman undergoing HAART to either a 12-week CBSM intervention (N=53) or to a wait-list control condition (N=49). Among the 102 enrolled a total of 71 participants underwent a social stress test (Trier Social Stress Test), which took place one month after termination of the CBSM course subsequent to post assessment.

The TSST consists of a job application speech and an unprepared mental arithmetic task performed in front of an audience. The CBSM consists of cognitive-behavioural stress-reducing techniques, assertiveness training, satisfaction of personal needs, strategies for using social support and self-management training.

Results: Findings indicated no differences in the endocrine stress reactivity of the HPA axis and SAMS. However we did detect that HAART, especially protease inhibitors (PI), had a profound impact on plasma cortisol and plasma noradrenalin stress response. Further, in a subgroup of patients without PI treatment, epinephrine response was reduced. Additionally, hemodynamic measurements revealed a significant difference in pulse pressure (PP), with reduced PP in the treatment group.

The CBSM training has no effect on coping behaviour and cognitive appraisal in the TSST, with exception of the primary scale “challenge” where the treatment group scored less.

Conclusion: PI-based regimens influence the stress reactivity and might interfere with possible treatment effects. Our findings demonstrate that CBSM training significantly diminished important cardiovascular risk factors. Thus the CBSM training might be a good method to reduce the risk of cardiovascular diseases in HIV infected population under HAART.

Figures and tables

List of abbreviations

ACTH	Adrenocorticotropic hormone
AIDS	Acquired immunodeficiency syndrome
ANS	Autonomic nervous system
AR	Adrenergic receptor
ART	Antiretroviral therapy
AVP	Arginine vasopressin
CA	Catecholamines
CAMP/PKA	Cyclic adenosine monophosphate/proteinkinase A
CBSM	cognitive behavioural stress management
CD4+ T lymphocytes	T helper cells expressing the surface protein CD4
CD8+ T lymphocytes	Cytotoxic T cell expressing the glycoprotein CD8
CMV	Cytomegalovirus or HHV-5
CNS	Central nervous system
DP	Double positive
CRH/CRF	Corticotropin-releasing hormone/ factor
DHEA-S	Dehydroepiandrosterone sulfate
DHEA	Dehydroepiandrosterone
DNA	deoxyribonucleic acid
E	Epinephrine
EBV	Epstein-Barr virus or HHV-4
EBV-VCA	Epstein-Barr virus viral capsid antigen
ECG	Electrocardiograms
Env	gene*: env*elope
GC	Glucocorticoid hormone
GH	Growth hormone
Gp120	Coat protein
HAART	Highly active antiretroviral therapies
HARS	HIV-1 associated adipose redistribution syndrome ()
HIV	Human immunodeficiency virus
HIV-1 RNA	Virus load
HPA	Hypothalamic-pituitary-adrenal
HSV	Herpes simplex virus
HSV-6	Human herpes virus-6
HSV-2	Herpes simplex virus type 2
IFNγ	Interferon γ
IgG	Immunoglobulin G

IL-2	Interleukine-2
iNOS	Inducible nitric oxide synthases = it uses the oxidative stress of NO to be used by macrophages in immune defence against pathogens
LD	Lipodystrophy
MAT	Medication adherence training
MBSR	Mindfulness-based stress reduction
mRNA	Messenger ribonucleic acid
MSH	Melanocyte-stimulating hormone
NE	Norepinephrine
NFκB	Nuclear factor kappa B = is a nuclear transcription factor
NK cell	Natural killer cell
NNRTI	Non-nucleoside analogue reverse transcriptase inhibitor
NO	Nitric oxide
NRTI	Nucleoside analogue reverse transcriptase inhibitors
OI	Opportunistic illnesses
PASA	Primary appraisal secondary appraisal scale,
PCD	Programmed cell death, apoptosis
PHA	Phytohaemagglutinin used as a mitogen to trigger synthesis in T-lymphocytes, and to activate latent HIV-1 from human peripheral lymphocytes
PI	Protease inhibitor
PNI	Psychoneuroimmunology
RIA	Radioimmunoassay
RNA	Ribonucleic acid, a single strand of genetic code
RT	Reverse transcriptase
SAMS	Sympatho-adreno-medullary system
SEBV	Skala zur Erfassung des Bewältigungsverhaltens
SHCS	Swiss HIV Cohort Study
SIV	Simian immunodeficiency virus
SIL	Squamous intraepithelial lesions
SNS	Sympathetic nervous system
SP	Single positive
SSG	Social Support Group
TNFα	Tumor necrosis factor α
TSST	Trier social stress test
UNAIDS	United Nations programme on HIV/AIDS
Vpr	Virion-associated accessory protein

1. Introduction

The development of highly active antiretroviral therapy (HAART) has changed the clinical disease pattern of HIV considerably (Potthoff & Brockmeyer, 2005) and has decreased the morbidity and mortality of HIV-1 infected patients (Egger et al., 1997). Thus HIV is now viewed as a chronic disease. Like other chronic diseases, the negative consequences of HIV infection and the use of medication might increase comorbid psychiatric disorders and physiological distress. Both are related to disease progression in HIV infected patients. Several studies have already demonstrated that emotional distress and stressful life experiences have an important impact on disease progression in HIV infected persons (Leserman, 2003a).

The relationship between chronic distress and disease vulnerability might be mediated via the direct psychophysiological pathway (Steptoe, 1991). Stress induced changes in endocrine, autonomic and immune function might influence health respectively disease progression in HIV. Current studies revealed that neuroendocrine and autonomic parameters are related to immunological alterations, which are related to disease progression in HIV (S. R. Cole et al., 2003; Leserman, 2003b).

Psychological interventions, such as group-based cognitive behavioural stress management (CBSM) training, have been shown to reduce distress and psychological symptoms in HIV infected patients in the pre-HAART era. Accompanying these psychosocial effects, changes in base physiological parameters such as cortisol, catecholamines, CD4+ T cells and NK cells could be shown (Antoni, Baggett et al., 1991; Antoni et al., 2002; Antoni, Cruess, Cruess, Kumar et al., 2000; Cruess et al., 1999; Cruess, Antoni, Kumar, & Schneiderman, 2000). In healthy male subjects CBSM influenced stress induced salivary cortisol response (Gaab et al., 2003; Hammerfald et al., 2006).

Therefore the purpose of this project was to evaluate the beneficial effect of a group-based CBSM training on the acute neuroendocrine (first paper) and autonomic stress reaction (second paper) and to answer the question if group-based CBSM training influences stress related physiological processes suggested to be indirectly related to HIV disease processes, such as activity and reactivity of the hypothalamus-pituitary axis and autonomic nervous system.

We randomly assigned 102 HIV patients to either a 12-week CBSM intervention (N=53) or to a wait list control condition (N=49). Of those, a total of 71 participants underwent a standardized psychosocial stress test (TSST: Trier Social Stress Test) (Kirschbaum, Pirke, & Hellhammer, 1993), which took place one month after completing the CBSM course.

The cognitive behavioural stress management training is based on the principles of stress inoculation training developed by Meichenbaum (Meichenbaum & Novaco, 1985) and modified according to F. H. Kanfer`s self management (Kanfer, Reinecker, & Schmelzer, 1996), K. Grawe`s psychological psychotherapy (Grawe, 2002) and the HIV group program developed within the scope of the EUROVIHTA project (Escobar Pinzón, 2000). The TSST consists of a job interview without prior preparation and a mental arithmetic task performed in front of an audience.

The findings of the hypothalamic-pituitary stress response (paper 1) indicated that CBSM has no effect on endocrine stress parameters. Protease inhibitors (PI) might have an influence on plasma cortisol and ACTH reactions as patients taking PI revealed a higher cortisol reaction than those with none and PI moderates the effect of ACTH response in the TSST.

The results of the sympathetic stress response (paper 2) revealed no differences in norepinephrine and epinephrine reaction in the TSST. However in a subgroup of patients assigned to CBSM with no PI in their treatment regimen, a reduced epinephrine response compared to the wait-list control group could be detected. Moreover we showed that patients in the CBSM group had a lower pulse pressure during the TSST compared to the control group.

The CBSM training has no effect on coping behaviour and cognitive appraisal in the TSST, with exception of the primary scale “challenge” where the treatment group scored less.

We concluded that CBSM might be a favourable intervention to reduce pulse pressure, an important cardiovascular risk factor, and might affect catecholamine response depending on HAART regimes.

In general PI treatment might have a profound impact of the stress reactivity in HIV infected persons, which might interfere with possible CBSM treatment effect.

2. Theoretical background

The following chapters focus on the essential concepts for the present two papers. Beginning with a description of HIV (human immunodeficiency virus) and the clinical implications of the virus for HIV infected persons, followed by the delineation of the stress paradigm and stress-HIV interaction. Concluding with a reflection on the possible influence of psychological interventions, with a special focus on cognitive behavioural stress management (CBSM) therapy, on biological parameters of the HIV disease.

2.1 HIV and clinical implications

The etiologic agent of acquired immunodeficiency syndrome (AIDS) is the human immunodeficiency virus (HIV). There are two known species of HIV that infect humans: HIV-1 discovered 1983 (Barre-Sinoussi et al., 1983; Gallo et al., 1983) and HIV-2 identified 1986 (Clavel et al., 1986).

The virus types resemble each other under electron microscopy, they both replicate in CD4+ T lymphocytes and have the same clinical course of infection. Differentiation is possible through the molecular weight of their proteins, as well as in their accessory genes. The following description focuses on the more frequently occurring HIV-1 infection. Three groups of HIV-1 have been identified on the basis of differences in *env* (gene*: env*elope*)*: M, N, and O (Thomson, Perez-Alvarez, & Najera, 2002). Group M is the most prevalent and subdivided into eight subtypes, based on the whole genome, that are each geographically distinct (J. K. Carr, Foley, B T, Leitner, T, Salminen, M, Korber, B and McCutchan, F, 1998).

HIV is a retrovirus classified as a member of the genus lentivirus (International Committee on Taxonomy of Viruses, 2006). Lentiviruses are characterised by a long chronic course of illnesses associated with a long period of incubation (clinical latency), persistent viral replication and involvement of the central nervous system (Levy, 1993). Like all retroviruses HIV stores its genetic material as RNA (ribonucleic acid) (Turner & Summers, 1999).

2.1.1 Pathogenesis of HIV infection

2.1.1.1 HIV replication cycle

HIV infects a variety of cells such as CD4+ T lymphocytes, macrophages, microglia and dendritic cells. The process of viral entry involves fusion of the viral envelope (*env* proteins gp120 and gp41) with the unit membrane, targeting host cells with specific surface receptors (CD4 or chemokine receptor (CCR5 or CXCR4)) (Stevenson, 2003). After fusing with the membrane an enzyme called reverse transcriptase (RT) converts viral RNA into a proviral DNA (deoxyribonucleic acid) copy (reverse transcription), which is integrated into the host's DNA (DNA integration). The HIV provirus (or integrated HIV DNA) is duplicated by normal cellular mechanisms each time the cell divides (viral replication). At the host cell membrane, the immature non-infectious virus buds off the cell and enters

the bloodstream (viral budding). The viral enzyme protease cuts the viral proteins in the forming bud or shortly after virus release to generate the mature HIV-1 virion. The mature virus is able to infect other cells (viral maturation) (Freed, 2001; Turner & Summers, 1999; Vigouroux et al., 1999).

2.1.1.2 Diagnostic criteria

The CDC classification system for HIV infections categorizes HIV infected adolescents and adults on the basis of clinical conditions associated with the HIV infection (categories A-C) and CD4+ T lymphocyte count to define the clinical stage (Centers for Disease Control, 1993).

Category A is described as an asymptomatic HIV infection with primary HIV infection or persistent generalized lymphadenopathy. Category B consists of symptomatic conditions that are attributed to HIV infection or are considered to require management that is complicated by the disease and are not included among conditions listed in clinical category C. Category C includes the clinical conditions listed in the AIDS surveillance case definition (Appendix B) (Centers for Disease Control, 1993).

The three categories corresponding to the CD4+ T lymphocyte count are defined as: category 1: ≥ 500 CD4 cells/μl; category 2: 200 to 499 CD4 cells/μl; category 3: < 200 CD4 cells/μl.

2.1.1.3 Clinical course of infection

Primary HIV-1 infection (viremia or acute infection) is typically defined as the time from virus entry to completion of seroconversion (Kassutto & Rosenberg, 2004). This stage is associated with a widespread dissemination of HIV viremia to lymphoid tissue, with an initial peak viremia of up to 1 million RNA molecules per millilitre (Kahn & Walker, 1998) and an abrupt decline of CD4+ T cells in the peripheral blood stream (Pantaleo, Graziosi, & Fauci, 1993). This is often (40-90% of patients) accompanied by the development of an acute retroviral syndrome (mononucleosis-like symptoms = febrile illness) 3 to 6 weeks after the initial infection (Kassutto & Rosenberg, 2004). A significant acute antiviral response of the immune system (increase in CD8+ cytotoxic T cells) suppresses viral replication (Koup et al., 1994; Pantaleo et al., 1994; Schmitz et al., 1999) and might be responsible for the marked reduction in viremia (between 6 and 12 weeks after infection) to a steady-state level of viral replication (clinical latency stage) (S. W. Cole & Kemeny, 1997; Kahn & Walker, 1998). The magnitude of the virus load set point, which occurs 6-12 month after infection, is a prognostic marker for disease progression (Lyles et al., 2000).

In the clinical latency stage (CDC Category B: median time is approximately 10 years) the HIV infection is associated with minor symptoms and low levels of HIV in circulation (S. W. Cole & Kemeny, 1997). However HIV continues to replicate in lymph nodes and other lymphatic organs and continues to infect CD4+ T cells (Pantaleo, Graziosi, Demarest et al., 1993) resulting in a progressive decline in the circulating level of CD4+ T lymphocytes. The course of CD4+ T lymphocyte decline is quite variable and its cause remains unclear.

With the progressive deterioration of the immune system (CD4+ T cell count drops below 200 cells/μl) the body becomes vulnerable to a variety of opportunistic infections and neoplastic diseases whose onset marks the occurrence of full-blown AIDS (CDC Category C) (S. W. Cole & Kemeny, 1997; Pantaleo et al., 1994).

2.1.2 Epidemiology

UNAIDS estimated that 38.6 million (33.4 million – 46.0 million) people worldwide were living with HIV at the end of 2005. In 2005 between 3.4 million and 6.2 million people became newly infected and an estimated 2.8 million (2.4 million -3.3 million) died from AIDS. Africa is still the global epicentre of the AIDS pandemic. In South Africa an estimated 5.5 million people (18,8% of adults) where living with HIV in 2005 (UNAIDS, 2006b).

In Switzerland approximately 20000-30000 persons have been infected since the beginning of the epidemic. The HIV incidence in 2005 was an estimated 708 cases, of whom 33.1% were women (Swiss Federal Office of Public Health, 2005) and 60 deaths from AIDS (2004) were reported (UNAIDS, 2006a)

About 51% of HIV infected patients in Switzerland are participants in the Swiss HIV cohort study (SHCS), a large prospective cohort study with 68% of all Swiss AIDS patients being registered in 2005 (SHCS, 2006).

As a consequence of improved therapy (highly active antiretroviral therapies, HAART) the death rate from the disease in areas where therapy is readily available has been reduced, e.g. the number of new AIDS cases and AIDS deaths in Switzerland has continuously declined approximately 80-90% since 1995 (Swiss Federal Office of Public Health, 2005; Zwahlen, Gebhardt, Rickenbach, & Egger, 2004).

AIDS has evolved into a horizontal epidemic in adults, spread by sexual contact or shared needles among drug addicts and into a vertical epidemic where the virus is transmitted from mother to child (Sepkowitz, 2001). In Europe and North America the proportion of heterosexually infected patients starting HAART in 2002-2003 increased to 47%, of whom 32% were women (Cohort Collaboration, 2006).

2.1.3 Highly active antiretroviral therapy

The course of HIV infection has changed dramatically since the beginning of the epidemic (Potthoff & Brockmeyer, 2005). The prognosis of HIV-1 infected patients has significantly improved since the use of highly active antiretroviral therapy (HAART) – a combination of at least three drugs, typically including either a protease inhibitor (PI) or a non-nucleoside analogue reverse transcriptase inhibitor (NNRTI) and two nucleoside analogue reverse transcriptase inhibitors (NRTI) (Badley, Pilon, Landay, & Lynch, 2000; Egger et al., 1997; Sterne et al., 2005). NNRTI bind to RT and NRTI block the growth of newly forming viral DNA, both prevent “reverse transcription”, whereas PI bind to the pro-

tease enzyme preventing "viral maturation" (Vigouroux et al., 1999). Before the implementation of HAART in 1996 only a single or dual antiretroviral therapy (ART) was used.

The efficacy of HAART in suppression of plasma HIV-1 RNA (virus load) and functional recovery of CD4+ T cell count has substantially decreased the morbidity and mortality of HIV-1 infected patients (Egger et al., 1997; Gulick et al., 1998; Hammer et al., 1997; Hogg et al., 1998; Ledergerber, Egger, Opravil et al., 1999; Mocroft et al., 1998; Palella et al., 1998). A recent study estimating the long-term effectiveness of HAART showed that antiretroviral therapy reduces the rate of progression to AIDS or death by 86% compared to untreated patients and by 51% compared to dual therapy (Sterne et al., 2005). Consequently currently HAART is a standard-of-care therapy (A. Carr & Cooper, 2000). Of the participants in SHCS more than 75% were receiving at least three drugs (SHCS, 2006).

However, a collaborative analysis (Cohort Collaboration, 2006) revealed no decline in the rate of AIDS or death up to 1-year follow-up parallel to virological improvements after starting HAART. In contrast the rate of AIDS increased in the most recent period (patient starting HAART in 2002-2003), which might be caused by changes in demographic characteristics of these patients (Cohort Collaboration, 2006).

Moreover AIDS related opportunistic illnesses (OI) continue to occur (Michelet et al., 1998). The risk of developing an OI while receiving potent therapy is highest during the first month of therapy and initial immunological and virological response to treatment were strong predictors of disease progression to AIDS or death (Chene et al., 2003; Ledergerber, Egger, Erard et al., 1999).

In addition viro-immunological discrepancies in response to antiretroviral treatment have been observed. Not all patients starting HAART do exhibit a significant increase in CD4+ T cell count parallel to HIV-1 RNA concentration (Badley et al., 2000; Grabar et al., 2000; Ledergerber, Egger, Opravil et al., 1999; Mocroft et al., 2000; Phillips et al., 2001). The pathological mechanisms leading to CD4+ T cell lymphopenia in HIV infection, as well as its effect on HAART, are still being discussed (Douek, Picker, & Koup, 2003; Gea-Banacloche & Clifford Lane, 1999). T cell apoptosis (programmed cell death) might be one of the mechanisms explaining CD4+ T cell lymphopenia (Badley et al., 2000; Douek et al., 2003; Roger et al., 1999; Roger et al., 2002; Sloand et al., 1999).

2.1.3.1 Side effects of HAART

HAART is accompanied by adverse metabolic effects and an increased risk of cardiovascular diseases (Kamin & Grinspoon, 2005; Monier & Wilcox, 2004; Wanke, Falutz, Shevitz, Phair, & Kotler, 2002). The "metabolic complications" include dyslipidemia, changes of body fat distribution, insulin resistance and glucose intolerance, metabolic bone disease and lactic acidosis (Amorosa & Tebas, 2006; A. Carr, Miller, Law, & Cooper, 2000; A. Carr, Samaras, Burton et al., 1998; Lo, Mulligan, Tai, Algren, & Schambelan, 1998; K. D. Miller et al., 1998; Monier & Wilcox, 2004; Walli et al., 1998).

Approximately 50% of all HAART treated patients develop at least one lipodystrophy (LD) related symptom after 12–18 months of therapy which is defined by a loss of subcutaneous fat and accumula-

tion of fat in the abdomen and nape of the neck ("buffalo hump"), in association with hypertriglyceridaemia and insulin resistance (A. Carr et al., 2000; Hogg et al., 1998; Koutkia & Grinspoon, 2004).
Although the relative risk factor for cardiovascular disease (hyperlipidemia, insulin resistance, change in body fat mass) increased in HAART treated patients, the relative risk of cardiovascular disease is still small in an absolute sense (Chene et al., 2003; Kamin & Grinspoon, 2005).
Beside metabolic distribution and an increasing risk of cardiovascular disease (S. K. Grinspoon, 2005) the use of HAART is also associated with further adverse reactions such as gastrointestinal side effects (Monkemuller, Lazenby, Lee, Loudon, & Wilcox, 2005), peripheral polyneuropathy (Simpson et al., 2006) renal problems (Valle & Haragsim, 2006), pancreatitis (Blanchard, Wohlfeiler, Canas, King, & Lonergan, 2003; Martinez et al., 2004) hepatotoxicity (S. Becker, 2004) allergies (Lin, Tucker, & Rieder, 2006), avascular necrosis (Cheonis, 2002) increased bleeding episodes in hemophiliacs (Wilde, 2000) abacavir hypersensitivity (Clay, 2002; Hewitt, 2002), neurocognitive impairment (Marcotte et al., 2003) and an increasing number of non-AIDS defining cancers (M. Bower, Palmieri, & Dhillon, 2006; Engels et al., 2005).
As a consequence of the amount of HAART side effects, the guidelines for HIV treatment tend to be conservative in contrast to the former “hit early, hit hart” strategy in consideration of a long term therapy (Monier & Wilcox, 2004; Sepkowitz, 2001; Yeni et al., 2002). Current studies focus on the effect of switching antiretroviral therapy regimes to prevent cardiovascular risk factors (Willard, 2006).

2.1.4 Hypothalamic-pituitary-adrenal (HPA) axis and HIV pathogenesis

Adrenal insufficiency is a well-established complication in HIV infection (Eledrisi & Verghese, 2001). Surprisingly, clinical manifestations of adrenal insufficiency are unusual in patients infected with HIV even though subclinical functional abnormalities of the HPA axis are frequent (Mayo, Collazos, Martinez, & Ibarra, 2002) and the adrenal gland is seen as one of the most compromised organs in patients with HIV (Rodrigues et al., 2002).
Autopsy studies in patients who died of AIDS revealed lesions of the adrenal glands in up to 99,2% of all examined cases (Bricaire, Marche, Zoubi, Regnier, & Saimot, 1988; Glasgow, Steinsapir, Anders, & Layfield, 1985; Groll et al., 1990; Pulakhandam & Dincsoy, 1990; Rodrigues et al., 2002; Tapper, Rotterdam, Lerner, Al'Khafaji, & Seitzman, 1984; Welch et al., 1984) and abnormalities of the pituitary gland in up to 32% of all cases (Groll et al., 1990; Sano et al., 1989).
However in clinical practice adrenal insufficiency is rarely diagnosed in HIV patients. The incidence of adrenal insufficiency in HIV infected patients is marginal 0.47% (Huang et al., 2004) 5-8% (Masharani & Schambelan, 1993) 9% (Raffi et al., 1991) and varies remarkably, depending on the criteria used to diagnose adrenal insufficiency (Marik, Kiminyo, & Zaloga, 2002).
One reason for the absence of clinical diagnostic of adrenal insufficiency is, that functional impairment in general population is first seen when almost 90% of the adrenal gland is destroyed (Eledrisi & Verghese, 2001). The lack of clinical suspicion is particularly due to mild primary adrenal insuffi-

ciency. These patients show non-specific symptoms and have a normal response to cosyntropin (Dorin, Qualls, & Crapo, 2003). In addition, symptoms suggesting adrenal insufficiency such as weakness, weight loss, hyponatremia, and hyperkalemia are common in patients at an advanced stage of HIV infection. They are not necessarily caused by adrenal insufficiency but by concurrent opportunistic diseases and treatment (Huang et al., 2004).

2.1.4.1 The influence of HIV on the HPA axis

Various studies have examined adrenal function in HIV infected patients. The results of these studies are inconsistent but they show, that subclinical functional abnormalities of the HPA axis are much more prevalent than clinical manifestation of these abnormalities (Eledrisi & Verghese, 2001).

Patients infected with HIV have been diagnosed with normal (Findling et al., 1994; Kertzner et al., 1993; Raffi et al., 1991) higher (Biglino et al., 1995; Christeff, Gharakhanian, Thobie, Rozenbaum, & Nunez, 1992; Membreno et al., 1987; Villette et al., 1990) or lower (Merenich, McDermott, Asp, Harrison, & Kidd, 1990) base cortisol levels than HIV seronegative individuals. These subtle defects in steroidogenesis are possibly due to abnormal stimulation of 18-hydroxydeoxycorticosterone in addition to other 17-deoxysteroids (Hofbauer & Heufelder, 1996) and selective impairment of 17-deoxysteroid production after adrenocorticotropic hormone (ACTH) stimulation (Oberfield et al., 1990). ACTH levels have been detected as elevated (Verges et al., 1989) normal (Membreno et al., 1987) or low (Biglino et al., 1995; Villette et al., 1990). Moreover an altered circadian rhythm of the pituitary gland and adrenocortical hormone secretion (Malone et al., 1992; Villette et al., 1990) and a significant reduction in cortisol secretion in response to ACTH stimulation (Freda & Bilezikian, 1999; Hoshino, Yamashita, Nakamura, & Iwamoto, 2002; Merenich et al., 1990; Verges et al., 1989) or normal cortisol levels (Dobs, Dempsey, Ladenson, & Polk, 1988) were observed. In response to corticotropin-releasing hormone (CRH) stimulation, ACTH level is normal and cortisol response is subnormal (Freda & Bilezikian, 1999; Lortholary et al., 1996) which lead to the suggestion that many asymptomatic patients with HIV infection may have early subclinical primary adrenal dysfunction (Freda & Bilezikian, 1999). Also, an observed exaggerated peak ACTH response accompanied by a normal cortisol response to CRH (Wilson, Truong, Barber, & Aoki, 1996) could be a very early indication of developing primary adrenal insufficiency (Freda & Bilezikian, 1999).

Further hormonal patterns exist in HIV infected patients showing the broad range of dysfunction in the course of the disease. For example elevated cortisol and ACTH (Norbiato et al., 1992; Verges et al., 1989), normal cortisol with elevated ACTH (Findling et al., 1994) or elevated cortisol despite low ACTH levels (Biglino et al., 1995; Eledrisi & Verghese, 2001; Villette et al., 1990).

One reason for the variability of reported basal and stimulated serum cortisol might be the progression stage to AIDS. Whereas in early stages of HIV infection endocrine dysfunction of the adrenal gland is rarely of clinical significance, it becomes more apparent and clinically manifest (related to cachexia and opportunistic infections) as the disease progresses (Eledrisi & Verghese, 2001; Freda & Bilez-

ikian, 1999; Mayo et al., 2002). In stage C of AIDS adrenal insufficiency was detected in 19% (Wolff et al., 2001) and 21 % (Marik et al., 2002) of all patients, using a cut-off point of ≥18 μg/dl as a normal cortisol response after a stimulation with 1 μg ACTH. Some authors supposed that in some instances, elevated serum cortisol levels might reflect stress adaption during the early stages of the disease (Christeff et al., 1992; Corley, 1996; Hofbauer & Heufelder, 1996; Norbiato et al., 1992; Verges et al., 1989).

Nevertheless, the adrenal gland represents a major endocrine target in HIV infection (Hofbauer & Heufelder, 1996). An infection with HIV is associated with many endocrine abnormalities, both in the early and later stages of AIDS (Freda & Bilezikian, 1999) and many subtle endocrine aberrations are evident very early in the course of HIV infection (Merenich et al., 1990) without becoming immediately clinically manifest.

Several potential etiologies of the endocrine disturbances associated with HIV infection have been described. Opportunistic infections were found to produce adrenal insufficiency as a result of primary adrenal infections (cytomegalovirus (CMV), *Mycobacterium avium-intracellulare* (MAI), tuberculosis, cryptococcosis, histoplasmosis, blastomycosis, toxoplasmosis, *Pneumocystis carinii)* and caused by secondary adrenal infection of the pituitary gland (CMV or toxoplasmosis) (Eledrisi & Verghese, 2001). Especially HIV patients with disseminated CMV infection have an increased risk of developing adrenal insufficiency (S. K. Grinspoon & Bilezikian, 1992). CMV is seen as the main cause of adrenalitis. 42,1% of all AIDS patients at an advanced stage with positive CMV antigenemia results showed abnormal rapid ACTH test, reflecting a significant correlation between CMV antigenemia and abnormal ACTH stimulation (Hoshino et al., 2002). Necrosis due to CMV was greater in the medulla than in the cortex (Glasgow et al., 1985).

Additionally, adrenal insufficiency is due to direct involvement of HIV, neoplasms (Kaposi sarcoma and lymphoma), hemorrhage, fibrosis, infarction and cortical lipid depletion reflecting long-lasting severe stress (S. K. Grinspoon & Bilezikian, 1992; Hofbauer & Heufelder, 1996; Leinung, Liporace, & Miller, 1995).

Finally, several medications can interfere with adrenal hormone blood levels by inhibiting adrenal steroidogenesis by blocking cholesterol desmolase, 11 beta-hydroxylase, and aldosterone synthase (Sonino, 1987) (ketoconazole) or enhancing cortisol metabolism (rifampin, phenytoin, and opiates). Megestrol acetate a synthetic progestogen that has been used in the management of AIDS related cachexia and anorexia has intrinsic glucocorticoid activity and suppresses the pituitary secretion of corticotropin. Prolonged administration can induce Cushing syndrome by secondary adrenal suppression (Eledrisi & Verghese, 2001; Hofbauer & Heufelder, 1996; Leinung et al., 1995; Padmanabhan & Rosenberg, 1998).

Adrenocortical antibodies have been detected in 45% of patients with AIDS (S. K. Grinspoon & Bilezikian, 1992; Hofbauer & Heufelder, 1996; Salim et al., 1988), which interfere with corticosteroid

action in vitro and could perhaps lead to peripheral resistance and clinical manifestations of cortisol deficiency (Eledrisi & Verghese, 2001). In consequence acquired peripheral cortisol resistance (elevated cortisol, reduction in the affinity of glucocorticoid receptors and lymphocyte resistance, low corticotropin state with paradoxical Addisonian features) (Norbiato et al., 1992) is seen as a further potential aetiology of the endocrine disturbances associated with HIV infection (Huang et al., 2004).

Moreover the pathogenetic potential of gp120 (coat protein) could be demonstrated in the central nervous system. Gp120 plays a key part in HIV associated nervous system impairment (Toggas et al., 1994) and may also be responsible for the change in activity of the HPA axis.

Corley hypothesized that the gp120-induced HPA axis activation may be mediated in part by an increase in IL1 within the hypothalamus (Corley, 1996). The "cortisol connection theory" (Corley, 1996) assumed that HIV uses a separate glucocorticoid metabolic route, which might be the basis of the cortisol excess seen in HIV. The theory presumes that peptide T subregion gp120 of HIV utilized MSH (melanocyte-stimulating hormone) receptors to competitively oppose the MSH-induced inhibition of IL-1. IL1 stimulates CD8+ T lymphocyte proliferation, as well as causing the release of CRH, thereby stimulating the release of ACTH and cortisol. Additionally gp120 induces upregulation of adrenocorticotrophic hormone-related messenger ribonucleic acid (mRNA). In consequence of the elevated cortisol, the glucocorticoid receptors will be reduced, which might induce cortisol resistance (Corley, 1996).

However the theory did not explain the precise molecular mechanism by which gp120 activates the stress-related peptides (Pozzoli et al., 2001). Thus further findings show that an increased activity of the HPA axis associated with HIV infection may be of central origin due to the effects of gp120 on hypothalamic CRH and arginine vasopressin (AVP) release in vitro and vivo (Costa et al., 2000). Expression of gp120 activates the HPA and thereby alters peripheral levels of immunomodulatory hormones (Raber et al., 1996). Gp120 might influence the HPA axis via the modulation of CRF synthesis. In vitro gp120 directly stimulates CRF gene expression and peptide synthesis of the rat hypothalamus via the activation of iNOS (inducible nitric oxide synthase) (Pozzoli et al., 2001). Finally the HIV-1 protein Vpr, a virion-associated accessory protein, could enhanced the effect of glucocorticoids on the target cells by acting as a GR coactivator in human lymphoid and muscle-derived cell lines (Kino et al., 1999).

Furthermore Smith (1992) reported HIV-induced ACTH production in T lymphocyte cells (Smith, Hughes, Hashemi, & Stefano, 1992). The HIV-induced ACTH was synthesized *de novo* and had the size and biological activity of pituitary ACTH. However the authors assumed that elevated ACTH might restrict HIV replication and possible infection because the inhibition of ACTH caused an increased viral expression (Hashemi, Hughes, & Smith, 1998).

In conclusion HIV is apparently a retrovirally induced genetic aberration of the glucocorticoid metabolism and may present a range of glucocorticoid imbalances, from cortisol resistance to cortisol excess (Corley, 1996). To date the mechanisms underlying this metabolic disturbance in HIV-patients are not fully understood. However hypercortisolemia is associated with more severe clinical and immunological outcomes (Christeff et al., 1997; Christeff, Melchior, de Truchis, Perronne, & Gougeon, 2002; Clerici et al., 2000; Leserman et al., 2002; Mayo et al., 2002).

2.1.4.2 The influence of HAART on the HPA-axis

A number of studies in the pre-HAART era demonstrate that hypercortisolemia (Christeff et al., 1992; Christeff et al., 1997; Mayo et al., 2002; Membreno et al., 1987; Verges et al., 1989; Villette et al., 1990) is a common adrenal dysfunction in HIV-infected individuals.

How and whether HAART modifies this profile is mostly unknown (Mayo et al., 2002). At present only a few studies have analysed the adrenal gland in HIV-infected patients under HAART (Christeff, De Truchis, Melchior, Perronne, & Gougeon, 2002; Christeff, Melchior, Mammes et al., 1999; Collazos, Ibarra, & Loureiro, 2004; Collazos, Mayo, Martinez, & Ibarra, 2003; Yanovski et al., 1999). The greater part of the studies indicates that HAART might increase cortisol levels (Collazos et al., 2003). Clinically stable HIV-infected patients receiving antiretroviral therapy usually had higher cortisol levels than untreated patients (Collazos et al., 2004; Collazos et al., 2003). Christeff (1999) detected increased cortisol levels in HIV-positive men on HAART and that the elevation of cortisol concentration in HIV-positive men compared to seronegative controls was independent of the treatment and stage of the infection (Christeff, Melchior, de Truchis et al., 1999; Christeff, Nunez, & Gougeon, 2000). In contrast one study indicates that cortisol concentration in HIV-patients with PI associated lipodystrophy (LD) was similar to healthy controls (Yanovski et al., 1999).

The increased use and duration of HAART treatment has made side effects (see chapter 2.1.3.1), especially LD, more evident. Although the distribution of fat accumulation in LD is similar to that induced by increased plasma glucocorticoid levels in Cushing's syndrome, the circulating cortisol concentrations are not elevated in LD patients (Biglino et al., 1995; Christeff, Melchior et al., 2002; Christeff, Melchior, de Truchis et al., 1999; Collazos et al., 2003; Koutkia & Grinspoon, 2004; Martin, Breen, & Weigle, 2003; K. K. Miller et al., 1998). Yanovski (1999) demonstrated that patients with PI-associated LD had normal diurnal cortisol secretion, cortisol secretory dynamics after the administration of ovine CRH, cortisol-binding globulin levels, and normal glucocorticoid receptor count and affinity in comparison to healthy controls (Yanovski et al., 1999). However 11β-HSD-1 mRNA is increased in adipose tissue of LD patients, which is supported by an elevated ratio of cortisol:cortisone metabolites in urine (i.e. in vivo conversion of cortisone to cortisol by 11β-HSD1 is enhanced) (Sutinen et al., 2004). The expression of the enzyme 11ß-hydroxysteroid dehydrogenase type 1 and of glucocorticoid receptors is elevated in omental fat compared to subcutaneous fat (Bujalska, Shimojo, Howie, & Stewart, 1997; Koutkia & Grinspoon, 2004; Rebuffe-Scrive, Anderson, Olbe, & Bjorntorp,

1990). Locally produced cortisol respectively increased glucocorticoid concentrations or action in adipose tissue without systematic hypercortisolism may induce regional adiposity (Koutkia & Grinspoon, 2004).

The particular combination of antiretroviral drug regimes has various influences on clinical side effects and physiological outcomes (Dube et al., 2005; P. N. Kumar et al., 2006; Willard, 2006). The majority of PI have been associated with the metabolic disturbances that constitute LD syndrome (A. Carr, 2000; K. D. Miller et al., 1998; Walli et al., 1998), especially ritonavir causes severe dyslipidemia (Fontas et al., 2004). Abnormal fat disposition was also detected in HIV-infected patients with non-PI-containing regimes, suggesting that other antiretroviral medications such as NRTI (e.g. staduvine) are linked with lipodystrophy (Kotler, Rosenbaum, Wang, & Pierson, 1999; Mayo et al., 2002; Saint-Marc et al., 1999; Vigouroux et al., 1999).

Cortisol levels were associated with NNRTI and PI, whereas NRTI seem to have no influence on cortisol serum levels (Collazos et al., 2004; Collazos et al., 2003; Saint-Marc et al., 1999). Collazos (2003) could demonstrate that NNRTI, especially patients on efavirenz (NNRTI) had significantly higher cortisol concentrations than those on nevirapine (NNRTI) and those treated with PI. The presence of antiretroviral therapy treatment with efavirenz (NNRTI) was a significant independent predictors of cortisol levels (Collazos et al., 2004). Additionally PI, in particularly ritonavir, are associated with higher cortisol levels (Collazos et al., 2004).

In contrast to cortisol concentration among patients receiving HAART, serum DHEA level was quite elevated in LD neg HAART-treated men, but it was significantly decreased in lipodystrophy pos HAART-treated men (Christeff, Melchior, de Truchis et al., 1999; Christeff et al., 2000). Consequently in HAART patients the cortisol/DHEA ratio was dramatically elevated in LD pos men compared to LD neg patients or healthy controls (Christeff, Melchior, de Truchis et al., 1999; Christeff et al., 2000). These results lead to the assumption that the modification in the cortisol/DHEA ration was mainly due to alteration of serum DHEA concentration because cortisol levels remained elevated (Christeff et al., 2000).

No significant correlation between cortisol and age, duration of HAART or CD4+ T cell count was found (Collazos et al., 2003). But the prior diagnosis of AIDS is significant independent predictors of cortisol levels (Collazos et al., 2004). Patients with past diagnosis of AIDS had significantly higher cortisol concentrations than patients without (Collazos et al., 2003). Furthermore patients with undetectable viral load had higher cortisol levels than patients with a detectable viral load (Collazos et al., 2003)

2.1.5 Autonomic nervous system (ANS) and HIV pathogenesis

Increasing evidence lead to the suggestion that HIV may alter the sympatho-vagal balance in HIV infected persons. Because of the longer survival of HIV patients through HAART more manifestations of late-stage HIV infection can be observed, which are related to autonomic dysregulations. The underlying mechanisms are currently the focus of investigations.

2.1.5.1 The influence of HIV on the sympatho-adrenomedullary system

Preceding studies already produced evidence of autonomic dysfunction in HIV-infected patients (J. A. Cohen & Laudenslager, 1989; J. A. Cohen, Miller, & Polish, 1991; Freeman, Roberts, Friedman, & Broadbridge, 1990; M. Kumar, Morgan, Szapocznik, & Eisdorfer, 1991), which might be present in the early stage of HIV infection and appears to progress to a significant decline in autonomic function during illness (Freeman et al., 1990; M. Kumar et al., 1991).

At present a number of syndromes related to HIV infection might be a sign of underlying autonomic dysfunction, which give rise to the hypothesis that HIV infection might influence the autonomic nervous system (Yun, Lee, & Bazar, 2004).

A variety of cardiovascular abnormalities such as myocardial, endocardial, pericardial and vascular diseases occur in HIV infected patients (see (Prendergast, 2003). Cardiac autonomic dysfunction in asymptomatic HIV infected patients ranges from 0-53% and from 13-100% in later HIV stages (Brownley et al., 2001), i.e. cardiac autonomic dysfunction increases with the disease's progression (K. Becker, Gorlach, Frieling, & Haussinger, 1997). The high prevalence of autonomic dysfunction is supported by abnormal hemodynamic and autonomic function tests performed with HIV infected persons (Brownley et al., 2001; Nzuobontane, Ngu, & Christopher, 2002; Yun et al., 2004). Particularly the pathogenesis of dilated cardiomyopathy, a common heart failure in HIV, is associated with alteration of sympathetic activity (Malfatto et al., 2001; Parthenakis et al., 2003; Yun et al., 2004) e.g. a reduced cardiac sympathetic innervation in heart failure is related to elevated levels of inflammatory cytokines (Parthenakis et al., 2003). Additionally, electrocardiograms (ECG) of HIV patients show a prolonged QT interval, which might be caused by adrenergic bias, possibly due to the infection (Yun et al., 2004). Adrenergic bias is also seen as a contributing factor to cachexia, a well-known gastrointestinal syndrome in HIV (Yun et al., 2004).

The mechanisms by which HIV infection induces autonomic imbalance have not been clearly established (Prendergast, 2003; Yun et al., 2004). Pathogenesis is still uncertain but several putative mechanisms are being discussed, including the suggestion that HIV may exhibit a cardiac tropism (Prendergast, 2003). Chen (2002) demonstrated that gp120 directly depressed contractility in myocytes in vitro (Chen et al., 2002). A current study detected that the HIV viral protein Vpr alters cardiomyocyte cell cycle events and causes defective contractility and atrial tumors (Lewis et al., 2005).

Beside the direct effects of HIV on cardiac myocytes, indirect effects of HIV mediated through immune-stimulated cytokine production are also discussed as potential mechanisms. For example gp120

enhancing IL-1β-induced nitric oxide (NO) production by cardiac myocytes is associated with the p38-mediated activation of NF-κB (Kan, Xie, & Finkel, 2000).

Opportunistic infections like Kaposi's syndrome or malignant lymphoma also have been reported to play a role in cardiovascular disease (Prendergast, 2003; Rerkpattanapipat, Wongpraparut, Jacobs, & Kotler, 2000).

Evidence of global autonomic dysfunction (decreased heart rate variability) in HIV-patients with (Neild, Amadi, Ponikowski, Coats, & Gazzard, 2000) or without AIDS (Mittal, Wig, Mishra, & Deepak, 2004) and no clinical heart disease were detected, concluding that HIV infection might be associated with autonomic dysfunction, independent of any heart disease. A feasible hypothesis for autonomic alteration might be that HIV influences the autonomic balance via the central nervous system (CNS), where HIV is localized in high concentration in the hypothalamic region (M. Kumar, Kumar, Waldrop, Antoni, & Eisdorfer, 2003), comparable to the direct activation of the HPA axis through the gp120 envelope protein (Clerici, Sarin et al., 1994; S. W. Cole & Kemeny, 1997; Raber et al., 1996; Yun et al., 2004).

2.1.5.2 The influence of HAART on the sympatho-adreno-medullary system

Another cause for autonomic imbalance, beside the suspected direct influence of HIV on the ANS, might be by the toxic effects of ART (Prendergast, 2003). Fliers (2003) proposed that HIV-1 associated adipose redistribution syndrome (HARS) is mediated by the effect of antiretroviral treatment in the CNS leading to regional changes in autonomic activity (increased norepinephrine concentration in skeletal muscle and subcutaneous fat tissue) (Fliers et al., 2003; van Gurp et al., 2006). Additionally an increased rate of lipolysis in HIV associated LD syndrome might possibly be caused by the change of catecholamine-stimulated lipolysis through the use of ritonavir (PI) (Adler-Wailes et al., 2005) indicating increased sympathetic activity (van der Valk et al., 2002).

Furthermore a high prevalence of multiple risk factors for cardiovascular diseases such as cholesterol levels, dyslipidaemia or elevated blood pressure etc. have been found to be associate with the use of antiretroviral therapies, especially the combination of NNRTI and PI drug classes (Friis-Moller et al., 2003; Glass et al., 2006; Hadigan et al., 2003; Sattler et al., 2001). A current study demonstrates elevated blood pressure after starting HAART, which might be important for the development of hypertension in long-term HAART use (Palacios et al., 2006).

The use of ART carries a risk of cardiovascular disease that increases by 16% for each year of exposure (Friis-Moller et al., 2003). While NNRTI and NRTI were not significantly associated with an increased risk, the use of PI did increase the risk of cardiovascular disease (Morse & Kovacs, 2006). It is expected that antiretroviral therapeutic drugs may induce cardiac dysfunction due to mitochondrial toxicity (Frerichs, Dingemans, & Brinkman, 2002; Lewis, 2000).

In detail the results of the DAD study indicated that the combination of antiretroviral therapy was independently associated with a 26% relative increase in the rate of myocardial infarction per year of

exposure during the first six years of use (Friis-Moller et al., 2003). However the estimated risk of myocardial infarction in relation to HAART in studies diverge, not all studies found a relation between the use of antiretroviral drugs and incidents of myocardial infarction (Bozzette, Ake, Tam, Chang, & Louis, 2003; D. F. Klein, 2002; Mary-Krause, Cotte, Simon, Partisani, & Costagliola, 2003; Morse & Kovacs, 2006).

In summary the findings suggest that multiple cardiovascular disease factors, as well as possible additional risks related to HAART use and underlying HIV infection might be responsible for autonomic imbalance in HIV infected persons.

2.2 Stress and the impact of stress on HIV progression

The development of HAART has transformed HIV into a treatable but not curable infection. Thus HIV is now viewed as a chronic disease. Like other chronic diseases, HIV infection and use of medication might increase comorbid psychiatric disorders and psychological distress. Both are related to disease progression in HIV infected patients. The relationship between chronic stress and disease vulnerability might be mediated via endocrine and autonomic stress response. This interaction will be described in the following section.

2.2.1 Definition of stress

Stress is defined as a state of threatened homeostasis, either real or perceived, which is re-established by a complex repertoire of physiological and behavioural adaptive responses of the organism (Charmandari, Tsigos, & Chrousos, 2005; Chrousos, 1998). These coordinated stress responses are composed of alterations in behaviour and mediators of adaptation such as the neuroendocrine system, autonomic nervous system and immune system referred to as allostasis, maintaining stability through change" (McEwen, 2003).

These changes are normally adaptive and alter the internal milieu to improve the individual's probability of survival (Charmandari et al., 2005). However an inadequate, excessive or prolonged stress response, e.g. a state of heightened activity of mediators, might lead to adverse effects on physiological functions or allostatic load. This is referred to as the "cost" of adaptation, the accumulation of wear and tear on physiological systems through adaptive processes (Charmandari et al., 2005; McEwen & Seeman, 1999).

2.2.2 Biological responses to stressors

The following passage focuses on the sympathetic nervous system (SNS) and the HPA axis which are the peripheral part of the stress system, whose main function is to maintain basal and stress-related homeostasis via catecholamines (CA) and glucocorticoids (GC).

2.2.2.1 Acute stress responses

A typical neuroendocrine stress response involves in the first wave an enhanced secretion of catecholamines within seconds (epinephrine and norepinephrine) from the sympathetic nervous system and adrenal medulla. The hypothalamus releases CRH and vasopressin from parvicellular neurons into the portal circulation and following 10 seconds later an increased release of pituitary ACTH. This response also involves decreased secretion of gonadotropin (pituitary gland) and increased secretion of prolactin and growth hormone (GH) (pituitary gland), renin (kidney) and glucacon (pancreas). In the second wave some minutes later, glucocorticoid hormone (GC) secretion is stimulated and the secretion of gonadal steroids is inhibited. 30 minutes and 1 hour after onset of a stressor, serum GC seems to reach peaks levels (Sapolsky, Romero, & Munck, 2000).

Thus, exposure to a stressor activates in particular the HPA axis and the sympatho-adreno-medullary system (SAMS), which has been described above in detail.

2.2.2.2 Physiology of the SAMS and HPA axis

The CRH-system and the locus ceruleus-NE/autonomic (sympathetic) nervous system, which are connected via neural projections providing a positive feedback loop, form the two central components of a stress response (Elenkov, Wilder, Chrousos, & Vizi, 2000) (see figure 1).

Sensory input passes through the thalamus, as a relay station, to the amygdala (Amiragova, 1985; Korte, Jaarsma, Luiten, & Bohus, 1992). Corticotropin-releasing factor neurons in the hypothalamic paraventricular nucleus receive input from the central amygdala, both directly and through the bed nucleus of the stria terminalis (Gray, 1993; Gray, Carney, & Magnuson, 1989). CRH is synthesized by the parvicellular neurons of the hypothalamic paraventricular nucleus and regulates the ACTH release from the anterior lobe of the pituitary gland (Carrasco & Van de Kar, 2003; R. L. Cole & Sawchenko, 2002). ACTH stimulates the cortex of the adrenal glands to produce androgen, aldosterone and glucocorticoid, mainly cortisol/corticosterone (Carrasco & Van de Kar, 2003). Cortisol effects are mediated by two glucocorticoid receptor subtypes: the mineralocorticoid and the glucocorticoid receptor (Carrasco & Van de Kar, 2003; Meijer & de Kloet, 1998).

Glucocorticoids play an important role in energy metabolism, growth processes, immune system and brain function, including learning and memory processes underlying behavioural adaptation (Carrasco & Van de Kar, 2003; Gesing et al., 2001; Stratakis & Chrousos, 1995). They also play a key regulatory role in the neuroendocrine control of the HPA axis and in the termination of a stress response by exerting a negative feedback on the hypothalamus and pituitary gland (de Kloet, 1995) as well as some supra-hypothalamic structures (Carrasco & Van de Kar, 2003; De Kloet, Sybesma, & Reul, 1986; Gesing et al., 2001; Meijer & de Kloet, 1998; Reul, Sutanto, van Eekelen, Rothuizen, & de Kloet, 1990).

Additionally corticotropin-releasing factor neurons project to noradrenergic cell bodies in the locus coeruleus (Carrasco & Van de Kar, 2003; Koob, 1999; Valentino, Foote, & Page, 1993). The activated LC-NE system results in increased norepinephrine (NE) levels throughout the brain, leading mainly to an enhanced arousal and vigilance (Carrasco & Van de Kar, 2003; Elenkov et al., 2000; Lavicky & Dunn, 1993). Peripherally the sympathetic (noradrenergic) system, a part of the ANS is activated, i.e. preganglionic efferent fibres leaving the CNS through the thoracic and lumbar spinal nerves are stimulated. The sympathetic preganglionic fibres (cholinergic) terminate in paravertebral or prevertebral ganglia. From these, postganglionic noradrenergic (i.e. NE releasing) sympathetic fibres innervate a wide variety of tissues and organs including smooth muscle of the vasculature, skeletal muscles, cardiovascular system, gastrointestinal tract, fat, primary (bone marrow and thymus) and secondary (spleen and lymph nodes) lymphoid tissues. The adrenal medulla of the suprarenal gland contains chromaffin cells and is innervated by preganglionic sympathetic fibres. These fibres release the neu-

rotransmitter NE, which is further converted to epinephrine (the approximate ratio is 1:4). Thus, the principal end products of the sympatho-adreno-medullary axis are the catecholamines NE and epinephrine (E) (Elenkov et al., 2000).

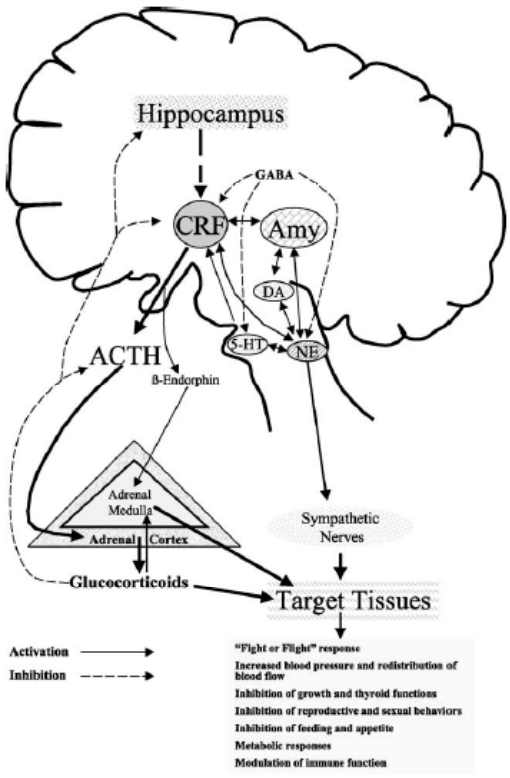

Fig. 1: The regulation of the neuroendocrine stress response (Carrasco & Van de Kar, 2003)

2.2.3 Stress and immune system

Over the time several models of the relationship between stress and immune system have arisen (Segerstrom & Miller, 2004). The most well known of these models assumed that chronic stress elicits simultaneous enhancement and suppression of the immune response by altering patterns of cytokine secretion (Agarwal & Marshall, 1998). Cytokines from CD4+ T_h1 cells promoting cell-mediated immunity (mainly IFN-γ, IL-2 and TNF-β) are suppressed, leading to a permissive effect on cytokines from CD4+ T_h2 cells, which in turn results in an activation of humoral immune factors (predominantly IL-4, IL-6, IL-10, IL-13) (Sapolsky et al., 2000; Segerstrom & Miller, 2004).

During infectious and psychological stress, the activation of the stress system through induction of a T_h2 shift may protect the organism against an overshooting immune system response, by selectively down regulating ongoing processes (Calcagni & Elenkov, 2006; S. W. Cole & Kemeny, 1997; Sapolsky et al., 2000; Schneiderman, Ironson, & Siegel, 2005).

Short-term "fight-or flight" stressors can therefore elicit potentially beneficial changes in the immune system. However the more chronic a stressor is, the more components of the immune system are affected. The elevated base levels of stress hormones associated with chronic stress suppress global im-

munosuppression (Schneiderman et al., 2005; Segerstrom & Miller, 2004).
HIV infection is characterised by progressively incapacitated CD4+ T lymphocytes, leading to an extreme imbalance in the immune system (see chapter 2.1.1) and consequently to an impaired self regulation. A further suppression of cellular immunity due to changes in cytokine patterns after chronic stress might lead to increased vulnerability of the immune system's self-regulation mechanisms and may have clinical consequences with regards to HIV progression (Segerstrom & Miller, 2004).
The interactions between stress and the immune system will be elaborated on in the next paragraphs.

2.2.3.1 Nervous-endocrine system and the immune system in healthy persons

A bidirectional communication network links the nervous-endocrine and immune systems. The CNS regulates the immune system via two major pathways, the hormonal response (e.g. HPA) and the autonomic nervous system through the release of NE and acetylcholine from sympathetic and parasympathetic neurons. In turn, the immune system can also regulate the CNS through cytokines (for rev. see(Eskandari, Webster, & Sternberg, 2003; Webster, Tonelli, & Sternberg, 2002).

HPA axis

The activation of the HPA axis has profound inhibitory effects on the body's immune/inflammatory response. Almost all components of the immune system are inhibited by GC (Charmandari et al., 2005). GC regulate a wide variety of immune system related genes, cell expressions and functions. For example, glucocorticoids modulate the expression of cytokines, adhesion molecules, chemoattractants and other inflammatory mediators and molecules, affecting immune cell trafficking, migration, maturation, and differentiation (Dhabhar, Miller, McEwen, & Spencer, 1995, 1996; Sapolsky et al., 2000).
Hence, the most general effect of GC is a reduction in activation and proliferation of T and B cells, causing a T_h1 to T_h2 shift in the immune response. GC suppress the T_h1 cytokine production of TNFα (tumor necrosis factor α), IFNγ (interferon γ) and IL2 (interleukin-2) directly in vivo and in vitro (Blotta, DeKruyff, & Umetsu, 1997; Elenkov, Papanicolaou, Wilder, & Chrousos, 1996). They also inhibit the production of IL12 which results in an increased IL4 and decreased IFN-γ secretion. Thus over both ways GC may influence the T_h1/T_h2 balance (Elenkov & Chrousos, 1999) which might lead to increased programmed cell death (PCD) (Clerici et al., 2000).
Interestingly GC mediate not only peripheral CD4+ cell numbers but also have been found to have an influence on earlier stages of differentiation. It was observed (Crompton, Ohashi, Schneider, Pircher, & MacDonald, 1992) that cortisone sensitive $CD3^{low}$ CD4 SP (single positive) thymocytes represent an intermediate stage in the transition from $CD3^{low}$ DP (double positive) to $CD3^{high}$ SP thymocytes and may have undergone positive selection events. Ge (1999) found seven discrete phenotypes of medullary CD4 SP lymphocytes. Two of them are cortisone sensitive, whereas the others were cortisone resistant (Ge & Chen, 1999).

An inflammatory stressor, which is associated with an immune challenge, causes a rapid immune activation that precedes adrenocortical activation and contributes to the subsequent increase in GC concentration. Various cytokines from activated immune cells work as mediators and can stimulate the adrenocortical axis (Besedovsky, del Rey, Sorkin, & Dinarello, 1986; Chrousos, 1995) e.g. via IL1 which influences the release of hypothalamic CRH (Sapolsky et al., 2000) and pituitary ACTH (Blalock, 1994). Cytokines such as IL-2, IL-6, TNFα and IFNγ can also activate the adrenocortical axis, though none has the potency of IL-1 (Sapolsky et al., 2000).
Furthermore the neuropeptide ACTH regulates directly some aspects of the immune system's function and vice versa cells of the immune system are known to synthesize ACTH (Blalock, 1994).

Sympathetic nervous system
The SNS plays a central role in the bidirectional regulatory relationship between the CNS and immune system. The SNS regulates the immune system at regional, local and systemic levels (S. W. Cole & Kemeny, 1997; Elenkov et al., 2000; Friedman & Irwin, 1997). For example during stress the activated ANS exerts systemic effects directly on immune organs innervated by sympathetic nerves and by inducing the secretion of IL-6 into systemic circulation (Ackerman, Felten, Dijkstra, Livnat, & Felten, 1989; Felten et al., 1987) which controls inflammation by stimulating glucocorticoid secretion (Charmandari et al., 2005; Mastorakos, Chrousos, & Weber, 1993).
Immune cells express neurotransmitter receptors, such as adrenergic receptors on lymphocytes that allow them to respond to neurotransmitters released from the SNS (Elenkov et al., 2000; Friedman & Irwin, 1997).
CA can also cause a selective suppression of T_h1 and enhanced T_h2 responses (Elenkov et al., 2000; Madden, Sanders, & Felten, 1995). CA inhibit production of proinflammatory cytokines, such as IL-12, TNF-α, and IFN-γ and stimulate the production of anti-inflammatory cytokines such as IL-10 and transforming growth factor β (TGF-β) (Elenkov & Chrousos, 1999).

Evidences indicated that the combined effects of GC and CA on the immune system during stress inhibit humorale immunity and T_h1 related cytokines but upregulates T_h2 related cytokine production.
Thus chronic dysregulation of the stress axis and consequently stress related imbalance of the immune system might be an important factor in disease progression in HIV disease (Segerstrom & Miller, 2004). Consequently both the HPA axis and the ANS might be possible mediators of the stress-immune relationship in HIV (Leserman, 2003b).

2.2.3.2 HPA axis and disease progression in HIV
Various possible mechanisms how glucocorticoid respectively catecholamine production might potentially affect the immune system in HIV disease and cause acceleration of disease progression are being discussed (Clerici et al., 2000; S. W. Cole & Kemeny, 1997; Nott, Vedhara, & Spickett, 1995). How-

ever little clinical evidence exists confirming the assumed pathways in vivo as only little research directly investigating the effects of SNS or HPA axis activation on pathological processes of HIV has been carried out.

Distress related endocrine changes might contribute to HIV progression either directly or through impact on the immune system.

Cortisol synergized with HIV peptide (gp 120) induces apoptosis in lymphocytes (M. P. N. Nair, Mahajan, Hou, Sweet, & Schwartz, 2000) and natural killer (NK) cell activity is synergistically inhibited by cortisol and HIV envelope peptide (env gag) (M. P. Nair & Schwartz, 1995). Furthermore GC have a potent effect on HIV replication, they have been found to accelerate HIV replication in infected T cells *in vitro*. HIV replication *in vitro* increases by the factor 2-5 in HIV infected peripheral mononuclear cells after applying hydrocortisone. This is possibly caused by indirect influence of GC on viral replication via cytokine alteration as no direct effect of GC on purified T cells was observed (Markham, Salahuddin, Veren, Orndorff, & Gallo, 1986).

As reported above, cortisol suppresses IFNγ and IL-2 production, increases IL-4 production and stimulates PGD (Clerici et al., 2000). A T_h1 to T_h2 cytokine shift in the course of HIV infection on single cell levels was demonstrated (S. A. Klein et al., 1997) also in HAART (Sindhu et al., 2006) and the reduction in the concentrations of some cytokines associated with the T_h1 profile have been linked to HIV progression (Clerici, Sarin et al., 1994; Clerici, Villa, & Shearer, 1994; Scott-Algara, Vuillier, Marasescu, de Saint Martin, & Dighiero, 1991). In contrast cortisol resistant patients show no cytokine shift, but a type 1 cytokine profile (Norbiato, Bevilacqua, & Vago, 1997).

Maybe elevated base cortisol levels due to HIV infection might cause greater stress related reductions in the ratio of T_h1/T_h2 cell derived cytokines and the number of CD8+ T cells and NK lymphocytes compared to healthy subjects with normal base cortisol production (Mayo et al., 2002). Favouring this mechanism, “HIV” and “stress” would use the same pathways, inducing a T_h2 cytokine shift and consequently disease progression (Elenkov 1999). However two studies refuted the shift in cytokine toward T_h2 (Graziosi et al., 1994; Maggi et al., 1994).

Under conditions of stress, cortisol has been associated with a decreased mitogen response and lower lymphocyte function in HIV patients (Antoni, Schneiderman et al., 1991; Goodkin et al., 1996) and high GC activity in combination with severe stress is associated with a lower number of killer lymphocytes (Leserman, 2003a; Leserman et al., 2000; Leserman et al., 2002; Petitto et al., 2000) demonstrated that 7.5 and 9 years after commencing the study, increases in cortisol were clearly and independently related to three markers of disease progression (AIDS, clinical AIDS condition, and mortality). For every 3 g/dl increase in cumulative average serum cortisol, there was a 40% increased risk of AIDS and about a 2.5-fold increased risk of developing an AIDS clinical symptom or dying from HIV infection (Leserman, 2003a; Leserman et al., 2000; Leserman et al., 2002). Increased plasma cortisol has also been linked to a social stressor in rhesus macaques and with accelerated simian immunodefi-

ciency virus (SIV) disease progression (Capitanio, Mendoza, Lerche, & Mason, 1998; Leserman, 2003a). There are some studies which did not find a link between HIV disease markers (CD4+ or CD8+ T lymphocytes) and cortisol in HIV (Gorman et al., 1991; Kertzner et al., 1993).
In addition a shift away from the androgen pathway toward cortisol production in HIV infected woman with wasting syndrome after endocrine stimulation is related to HIV disease markers (S. Grinspoon, Corcoran, Stanley, Rabe, & Wilkie, 2001). HIV infected patients showed lower levels of dehydroepiandrosterone (DHEA) (Christeff et al., 1997; de la Torre, von Krogh, Svensson, & Holmberg, 1997; Freda & Bilezikian, 1999; Wisniewski, Hilton, Morse, & Svec, 1993), which is viewed as a cortisol antagonist (Hechter, Grossman, & Chatterton, 1997; Wolf & Kirschbaum, 1999). Christeff (1997) found that CD4+ T cell counts were negatively associated with serum cortisol and positively related to serum DHEA. Thus both decreased levels of DHEA and increased cortisol/DHEA ratio have been associated with progression to AIDS and might be an independent predictor of HIV progression (Christeff et al., 1997; Ferrando, Rabkin, & Poretsky, 1999; Laudat et al., 1995; J. W. Mulder et al., 1992). DHEA treatment has no significant effects on HIV disease markers (Rabkin, McElhiney, Rabkin, McGrath, & Ferrando, 2006). However the adrenal 11β-hydroxylase-blocker metyrapone can shift adrenal metabolism toward androgen production and might reverse a potentially maladaptive stress response (Koutkia, Berry, Eaton, Breu, & Grinspoon, 2006).

2.2.3.3 SAMS and disease progression in HIV

A few hypothesis how catecholamine production might influence the immune system and hasten HIV progression are also in discussion (Clerici, Sarin et al., 1994; S. W. Cole & Kemeny, 1997; Nott et al., 1995). Again clinical evidence verifying the proposed pathways is rare.

In vitro the ANS neurotransmitter NE and other cAMP/PKA (cyclic adenosine monophosphate/proteinkinase A) activators have been shown to accelerate HIV replication and the cellular expression of HIV co-receptors and HIV gene expression (Chowdhury et al., 1993; S. R. Cole et al., 2003; S. W. Cole, Jamieson, & Zack, 1999; Nokta & Pollard, 1992) suggesting that the effect of NE on viral replication is transduced via the β-AR (adrenoreceptor)-adenylyl cyclase-cAMP-PKA (protein kinase A). Furthermore Cole (1998) could demonstrate that HIV replication caused by NE is mediated via a marked suppression of IFN-γ and IL-10 (T_h1) and via stimulation of β_2 AR (adrenergic receptor). The cytokines TNF-α, IL-1β, IL-2, IL-4 and IL6 were mildly suppressed by NE whereas the production of IL-12 was not altered, supporting a T_h1 to T_h2 shift (S. W. Cole, Korin, Fahey, & Zack, 1998).
In vivo Cole (2001) demonstrated that high ANS activity is related to a poor response to HAART therapy. Higher activity of the ANS was associated with higher viral load and a slower CD4+ cell recovery after patients were treated with HAART. This suggests that CA have a direct effect of HIV progression (S. W. Cole et al., 2001).

In contrast Moriuchi (2006) found that NE appears to suppress HIV replication in vitro (acute) and ex vivo (endogenous) through the NFκB inactivation (Moriuchi, Yoshimine, Oishi, & Moriuchi, 2006).
SNS activation may also influence HIV progression indirectly by interfering with the immune system's control of co-infections or opportunistic pathogens (S. W. Cole & Kemeny, 1997). Activation of several viruses (e.g. CMV, Epstein-Barr virus (EBV), herpes simplex virus (HSV) and human herpes virus-6 (HHV-6)) has been shown to heighten HIV virion replication (Lusso & Gallo, 1995). Altered autonomic dysfunctions in HIV infection are also related with increased HAART side effects (Rogstad, Shah, Tesfaladet, Abdullah, & Ahmed-Jushuf, 1999; Wulff, Wang, & Simpson, 2000). Furthermore NE can contribute to the pathogenesis of AIDS related cardiovascular diseases by enhancing leukocyte adhesion to cardiac capillary endothelial cells (HMVEC-Cs) (Sundstrom et al., 2003).
Under acute stress no difference in CA response (Hurwitz et al., 2005), heart rate, blood pressure and plasma cortisol (Hengge, Reimann, Schafer, & Goos, 2003; Hurwitz et al., 2005) could be detected between HIV infected persons and healthy controls, however immune reactions differ (Hengge et al., 2003; Hurwitz et al., 2005). HIV infected persons displayed greater lymphocytosis per unit in norepinephrine compared to HIV negative subjects, whereas NK cell reactivity was positively related to epinephrine responsiveness only in healthy control groups, which might reflect a pathophysiological alteration in sympathoimmune communication (Hurwitz et al., 2005). In particular with regard to the theory that NK cell mobilization might be a functionally relevant component of the "fight or flight" response aimed to protect the organism in situations of acute stress (Bosch, Berntson, Cacioppo, & Marucha, 2005).

It is important to keep in mind that the causal direction of a change in cortisol or CA during the disease's progression remains unclear as an increase in cortisol or CA may be a result or cause of an accelerated disease progression (Leserman, 2003b).

2.2.4 Psychosocial predictors of disease progression in HIV

The HIV disease progression is highly variable among individuals. However the factors known to play a role in determining the rate of progression e.g. the viral strain, genetic characteristics of the host immune system, co-infections with other pathogenic organisms and health maintenance habits can't explain the extreme degree of variability noted in the course of HIV disease adequately (S. W. Cole & Kemeny, 1997).
In consideration of the fact that certain immune parameters are modulated by physiological mediators of the stress response (i.e., catecholamines and glucocorticoid hormones), it is only logical to investigate the role of psychosocial characteristics (e.g. stress, social isolation, depression etc.) in the progression of HIV infection. Especially as considerable evidence linking psychological stress immune system dysregulation and HIV progression has been documented (S. W. Cole & Kemeny, 1997; Miller

& Cohen, 2001). In the next few paragraphs two psychosocial characteristics, "stressful life experiences" and "depression", which may influence disease progression in HIV, will be discussed.

2.2.4.1 Stressful life experiences

Studies examining stressful life events and their impact of HIV progression have shown conflicting results. Strong evidence for the role of life stress in HIV disease progression comes from the longitudinal CHIP study (Coping in Health and Illness Projects) of asymptomatic, HIV positive, gay men (Evans et al., 1995; Evans et al., 1997; Leserman et al., 2000; Leserman et al., 2002; Leserman et al., 1997). They consistently reported that stressful life events have adverse effects on the health of HIV infected patients.

Men with more severe stressful life events at baseline had lower NK cell counts (CD16+ and CD56+) and fewer cytotoxic/suppressor cells (CD8+ T lymphocytes) compared to men with less stress (Evans et al., 1995). Severe stress was related to a greater decline in CD8+ T cells and CD16+ NK cells at 2-years follow-up and stress effects were more pronounced among those with more severe symptoms of depression (Leserman et al., 1997) i.e. subjects who scored above the median on stress and depression were most likely to show a decline of immune parameters.

Moreover the risk of HIV disease progression at a follow-up 3.5 years later (e.g. drop in CD4+ T cells or development of HIV clinical symptoms) was doubled with every severe stressor per 6-month interval (Evans et al., 1997). At 5.5 (Leserman et al., 1999), 7.5 (Leserman et al., 2000), and 9 years (Leserman et al., 2002) of follow-up, higher average cumulative stressful events were predictive of faster progression to AIDS. At all follow-ups the risk of AIDS was approximately doubled and the risk of clinical AIDS condition was approximately tripled after 9 years for every cumulative average increase of one severe stressor.

Ironson (1994) found that men with greater distress at the time of HIV serostatus notification had a greater risk of HIV related clinical symptoms at a 2-year follow-up (Ironson et al., 1994).

HIV infected homosexual men with less severe life adversity and less depression had a lower likelihood of having an increased percentage of CD4+ cells at a 6-month follow-up (Patterson et al., 1995). Further findings indicate that high distress is associated with decreased numbers of T_h cells and B cells, but only at low levels of viral burden (Motivala et al., 2003).

African Americans with traumatic HIV exposure, particularly among those with posttraumatic stress disorder, were associated with greater decreases in the CD4/CD8 ratio during 1-year follow-up (Kimerling et al., 1999). Howland et al. (2000) showed that two or more stressful life events (e.g. death, major illness, or loss of family member etc.) in children and adolescents were associated with almost a three-fold increased risk of reduced CD4+ count during 1-year follow-up (Howland et al., 2000).

HIV progression has also been negatively linked to life stressors such as bereavement, which was related to a subsequent CD4+ cell decline over 3-4 years. However, bereavement did not predict pro-

gression to AIDS or mortality rate (M. E. Kemeny & Dean, 1995). Goodkin (1996) demonstrated in a 6 month study that bereaved HIV infected men had lower NK cell cytoxicity and lymphocyte proliferation response to PHA (phytohaemagglutinin) than non-bereaved persons (Goodkin et al., 1996). Those who found meaning in bereavement showed a less rapid reduction in CD4+ cell levels and lower rates of mortality (J. E. Bower, Kemeny, Taylor, & Fahey, 1998).

Life stress has also been examined as a possible co-factor in the initiation and progression of further diseases common with HIV infected patients. Stress might be a significant predictor of genital herpes (Herpes simplex virus type 2, HSV-2) (Pereira, Antoni, Danielson, Simon, Efantis-Potter, Carver, Duran, Ironson, Klimas, Fletcher et al., 2003) and was observed to be an independent risk factor of squamous intraepithelial lesions (SIL) in women with HIV (Pereira, Antoni, Danielson, Simon, Efantis-Potter, Carver, Duran, Ironson, Klimas, & O'Sullivan, 2003).

The evidence for an impact of life stress on AIDS progression is not uniformly found. Kessler (1991) found no association between the frequency of life stressors and either a decline in CD4+ cell count, or the development of symptoms among initially asymptomatic HIV positive gay men (Kessler et al., 1991).

Rabkin (1991) also detected no relationship between the number of negative life events and a change in CD4+ and CD8+ cell count over the following 6 months but did find a suggestive relationship between distress (anxiety and depression) and symptom development (Rabkin et al., 1991). Additionally Perry (1992) could not detect a correlation of CD4+ cell counts and stressful life events (Perry, Fishman, Jacobsberg, & Frances, 1992).

However studies examining subjects over longer periods and actual stressors (e.g., bereavement etc.) or using contextual based interviews rather than stress assessments by questionnaire show more reliable results (Leserman, 2003a).

Interestingly, even though elevated distress levels have been shown to be related to increased cortisol in numerous populations and among HIV infected persons in particular (Gorman et al., 1991), Leserman (2000) could determine neither a relationship between cortisol and stressful events, nor that cortisol levels mediated the increased risk associated with stressful life experiences. The fact that cortisol levels independently predicted disease progression, lead to the assumption that cortisol might use other pathways to affect the immune system (Leserman et al., 2000).

2.2.4.2 Depression and distress

Depression is the most common psychiatric disorder in HIV. Persons with HIV have a 2-fold greater risk of major depression than HIV negative control subjects (Ciesla and Roberts 2001) with woman being more likely to have a depression (Ciesla and Roberts 2001, Morrison 2002, Rabkin 1997).

Endocrine abnormalities such as hypercortisolism are associated with depression and might alter the immune system's functioning (Leserman 2003, Pepitto 2000) and contribute to HIV induced depression.

Thus the effects of depression as a possible mechanism related to variation in HIV progression was investigated in a number of studies. Some of them yielded significant association between depression and immune parameters, while others came to the opposite conclusion.

No significant relationship between depression and the HIV disease stage was detected in 2 studies across 6-12 months (Perry et al., 1992; Rabkin et al., 1991) and a meta-analysis (Zorrilla, McKay, Luborsky, & Schmidt, 1996).

Furthermore Lyketsos (1993) found no significant relationship between depression and indicators of HIV disease progression, AIDS or mortality after 8 years follow-up (Lyketsos et al., 1993).

In contrast Burack (1993) reported findings of a 5-year prospective cohort study that showed a significant correlation between depressive symptoms and a more rapid decline in CD4+ T lymphocyte count, although not with increased HIV/AIDS-related morbidity or mortality (Burack et al., 1993).

After 7 years of follow-up in the same cohort, men with elevated depression at each visit had a 1.67-fold greater risk of mortality compared to men who never had depression (Mayne, Vittinghoff, Chesney, Barrett, & Coates, 1996).

In addition, persons entering the cohort study with an already manifest depression had a faster progression to AIDS (1.76 greater risk) in comparison to men who never had elevated depression at 9 years follow-up (Page-Shafer et al 1996). In a further study Patterson (1995) concluded that depressive symptoms were associated with a more rapid mortality but not with a change in CD4+ cell count or progression to AIDS (Patterson et al., 1995).

Analyses of the CHIP study results (Leserman et al., 1999; Leserman et al., 2000; Leserman et al., 2002; Leserman et al., 1997) demonstrated a relation between depressive symptoms and a greater decrease in several lymphocyte subsets, especially among persons with more stressful events after 2 years follow-up. After 5.5 and 9 years follow-up (1999, 2002) the risk of AIDS was approximately doubled for every cumulative average increase of one severe depressive symptom. However after 7.5 (Leserman et al., 2000) and 9 years follow-up depressive symptoms were not associated with AIDS progression.

Depression might increase in later stages of HIV infection. Lyketsos (1996) reported that depressive symptoms increase 1.5 years before AIDS diagnosis (Lyketsos et al., 1996). Likewise Solano (1993) found that psychological distress predicted development of symptoms only in the group with low initial CD4+ cell count (Solano et al., 1993). In contrast (Burack et al., 1993) detected a more rapid decrease in CD4+ counts associated with depression in patients with high CD4+ cell counts.

Kemeny (1990) proposed that the duration of depression might be of importance (M. Kemeny, Duran, & Taylor, 1990). Sustained depression over a 2-year period was related to a faster decrease in CD4+

counts compared to non-chronically depressed subjects (Balbin, Ironson, & Solomon, 1999). Chronic depressive symptoms in woman were associated with a doubled risk of death and greater decline in CD4+ cell count compared to women with limited or no depressive symptoms over a 7-year period (Ickovics et al., 2001). AIDS related deaths were more likely among HIV positive women with chronic depressive symptoms and the symptoms were more severe among women in the terminal phase of their illness (Cook et al., 2004).

Even during the era of HAART a longitudinal study found an association between depression at baseline, CD4+ cell count and viral load (Ironson et al., 2005). A decrease in depression is associated with increases in NK cell activity over time (Cruess, Douglas et al., 2003).

The inconsistent results across these studies might result from the use of different methodologies (study design, assessment protocol, immune measures) (Cruess, Petitto et al., 2003). A robust relationship between depression and HIV disease progression is primarily seen in longitudinal studies, which are conducted over long periods and studies analysing chronic effects of depression.

In summary depressive symptoms are mostly related to disease progression, respectively parameters important for disease progression. However it is not clear whether depression is a predictor or a result of disease progression (Leserman, 2003b).

2.3 Behavioural intervention in HIV

As reported above, the hypothalamic pituitary adrenocortical and sympathoadrenomedullary axes are responsive to stress and may become dysregulated under conditions of chronic disease stress (Chrousos 1992). Thus alteration of the stress response systems by interventions might reduce the burden or allostatic load caused by the stress response (Seeman & McEwen, 1996) and possibly result in a healthy equilibrium of neuroendocrine and immune function.

2.3.1 Coping and disease progression in HIV

How people cope with stress may alter the course of HIV-1 infection. Some investigations have focused on the relationship between style of coping, such as active confrontational coping versus denial or disengagement, and health in HIV.

Persons who cope with stressful events by finding meaning or by being less distressed had fewer symptoms and higher CD4+ lymphocyte counts.

Ironson (1994) demonstrated that reacting with denial and behavioural disengagement from pre- to postserostatus notification was related to a greater CD4+ cell count decline and lowered T cell proliferation response after 1-year follow-up and with a greater likelihood of symptoms or death at 2-year follow-up (Ironson et al., 1994). Similarly, HIV-infected gay men with high passive coping (eg, behavioral and mental disengagement and denial) had lower CD4/CD8 ratios and a lower lymphocyte proliferative response to PHA at 3 weeks and 1 year after serostatus notification compared to those with low passive coping (C. L. Mulder, Antoni, Duivenvoorden, Kauffmann, & Goodkin, 1995) and HIV infected subjects with higher denial and lower “fighting spirit” at baseline. These individuals were more likely to develop symptoms of AIDS over a 1-year period (Solano et al., 1993). Leserman (2000) showed faster progression to AIDS during 7.5 years in subjects with high denial coping (Leserman et al., 2000). Moreover HIV infected children, who disclosed their HIV status to their friends during the study year were more likely to have increases in CD4+ percentage (B. F. Sherman, Bonanno, Wiener, & Battles, 2000). In contrast Mulder (1999) found that avoidance coping was associated with a lower rate of CD4+ cell count decline over 7 years (C. L. Mulder, de Vroome, van Griensven, Antoni, & Sandfort, 1999).

Some studies concluded that active coping is associated with better disease outcomes in HIV. Active, optimistic coping behaviour was negatively related to mortality over 1-7 years (Blomkvist et al., 1994). Further, active confrontational coping (measurement by seeking support, problem solving, and less denial) was associated with decreased clinical progression at 1-year follow-up (C. L. Mulder, Antoni, Duivenvoorden et al., 1995), whereas HIV positive individuals with less active problem-related coping (positive re-appraisal, seeking social support) were more likely to develop AIDS (Balbin et al., 1999; Vassend, Eskild, & Halvorsen, 1997).

Other studies have investigated the influence of mindset such as pessimism and optimism throughout HIV progression. Segerstrom (1996) showed that the tendency to attribute negative events to the self

was predictive of faster CD4+ lymphocyte decline over the 18-month study period (Segerstrom, Taylor, Kemeny, Reed, & Visscher, 1996). More negative or pessimistic HIV related health expectations augment the risk of developing HIV related symptoms after 3 years in patients with a previous HIV/AIDS experience (e.g. who had lost a friend or partner to AIDS) (Reed, Kemeny, Taylor, & Visscher, 1999). In contrast to negative mindset, which is related to faster disease progression, positive mindset is protective (Balbin et al., 1999), as an optimistic outlook was associated with lower mortality (Blomkvist et al., 1994). However an optimistic disposition was related to a decrease in CD4+ cell count (Tomakowsky, Lumley, Markowitz, & Frank, 2001), which may be explained by the fact that the effects of dispositional optimism depend on the severity of the stressor and might be maladaptive i.e. a decrease in immune measures, when the stressor is difficult (Segerstrom, 2005).

In summary the results indicate that active coping strategies are more beneficial to health in HIV infected individuals, whereas a passive coping style increases the rate of progression. Thus the style of coping might be one factor contributing to the variance in HIV disease progression.

According to these findings, the development and use of adaptive coping strategies to deal with daily stress and the stress of a chronic life-threatening illness are required for an improved health.

2.3.2 Cognitive-behavioural stress management training

Studies have demonstrated that the way of coping with stress may alter the course of HIV progression (s. above) (Ironson et al., 1994; Leserman et al., 2000; Leserman et al., 2002; C. L. Mulder, Antoni, Duivenvoorden et al., 1995; Solano et al., 1993).

The fact that stress and coping are related to HIV disease progression and coping styles can be predictive of disease outcome makes it obvious to use intervention with the aim to reduce stress and develop coping strategies to improve immune markers and if possible health markers in HIV disease.

2.3.2.1 Theoretical background of CBSM

In our study we used a cognitive-behavioural stress management training (CBSM), which is based on the principles of stress inoculation training developed by Meichenbaum (Meichenbaum & Novaco, 1985) and modified according to F. H. Kanfer`s self management, K. Grawe`s psychological psychotherapy and the HIV group program developed within the scope of the EUROVIHTA-project (Escobar Pinzón, 2000; Grawe, 2002; Kanfer FH, Reinecker H, & D., 1996). CBSM is based on theoretical principles of the transactional stress model first described by (Lazarus & Folkman, 1984).

In this model coping is considered a cognitive and behavioural effort to manage external and/or internal demands that are perceived as taxing or exceeding the resources of the person. These efforts are always changing as a function of continuous appraisals and reappraisals of the person-environment relationship (Folkman & Lazarus, 1988). According to this approach, the stress experienced in a given situation is determined through an evaluative process referred to as cognitive appraisal.

There are two forms of appraisal, primary and secondary. In "appraisal of the situation" (primary appraisal) the person answers to the question "What do I have at stake in this encounter?". Emotion quality and intensity depend on the answer to this question.
The "appraisal of coping resources" or the question "What can I do about this situation?" is labelled "secondary appraisal" (Lazarus, 1966). This answer influences the kind of coping strategies that will be needed to manage the situation.
In the transactional model coping has two main functions defined by (Lazarus, DeLongis, Folkman, & Gruen, 1985).
These have been called problem-focused coping (to manage or alter the source of stress) and emotional-focused coping (to regulate the emotional response).
Consequently stress is neither a personal trait or environmental nor stimulus or reaction (Meichenbaum, 2003), it is a specific bidirectional, always changing relationship between person and environment, a result of a transaction (Folkman, 1984). In detail, stress occurs if the situation poses a threat to the person's valued goals or well-being and the demand of the situation exceeds the person's resources for coping. In this process coping is considered a mediator of the emotional response in the way that primary appraisal influences coping, which in turn changes the person-environment relationship and therefore the emotional response (Folkman & Lazarus, 1988).

Appraisals of person-environment relationships are influenced on the one hand by antecedent personal characteristics (e.g. motivation, self image, recognition of personal resources for coping) and on the other hand by environmental variables (e.g. nature of the danger, ambiguity and duration) (Folkman & Lazarus, 1988).
Individual differences in characteristics explain why the same situation may be appraised as a threat, as neutral or as a challenge by different personalities (Folkman & Lazarus, 1988). Moreover as initial reported, the particular style of stress appraisal and coping may be associated with increased symptoms and disability in diseases (see chapter 2.3.1).

Therefore CBSM has the aim to change people's coping resources and consequently their emotions respectively stress reactions.
Our intervention consisted of cognitive-behavioural stress-reducing techniques (cognitive restructuring, problem-solving, self-instruction), assertiveness training, satisfaction of personal needs, strategies for using social support, self-management training and progressive muscle relaxation (Jacobsen & Höfler, 2002).
These techniques reinforce intra and interpersonal coping strategies, increasing the possibility of an adaptive response to a situation i.e. the coping strategies match the situation. This is a key factor in coping effectiveness (Lazarus & Folkman, 1984).

More precisely the stress-techniques might modify the way that stressful circumstances are appraised, helping the person to view the circumstances as less threatening (e.g. cognitive restructuring). They might target negative emotions directly through activities like relaxation and apart from the stress-reduction functions they might directly change behaviour such as an increase in social contact (Miller & Cohen, 2001).

All these techniques are intended to change the dynamic mutually reciprocal relationship between emotions and coping insofar that a person experiences less distress and subsequently fewer negative emotional states. This is hypothesized to modulate the immune system by activating the sympathetic nervous system, thereby interrupting the hypothalamic-pituitary-adrenal axis (Miller & Cohen, 2001) (see chapter 2.2.3).

A number of studies have demonstrated the effectiveness of CBSM reducing symptoms of distress and biological outcomes among healthy and HIV-infected persons.

2.3.2.2 CBSM in healthy subjects

Some examinations in the project group surrounding Gaab (2003) had demonstrated that CBSM reduces psychological stress and improves stress-related coping strategies. In healthy subjects (Gaab et al., 2003) demonstrated a reduced neuroendocrine stress answer to an acute stressor among those participating in a short group-based CBSM training. Subjects in the CBSM group showed an attenuated free cortisol stress response, which was influenced by differences in coping strategy. CBSM participants appraised the stress situation as less stressful and had an improved self-concept of their own competence (Gaab et al., 2003).

The positive effect of CBSM on psychosocial stress could also be detected in a natural stress situation. On the day of an academic exam, healthy students who took part in CBSM training revealed an attenuated cortisol awakening profile compared to the control group. Additionally in the CBSM group cognitive appraisal stress was strongly associated with the integrated stress response, however this relationship was not observed in the control group (Gaab, Sonderegger, Scherrer, & Ehlert, 2006). A previous study already concluded that cognitive appraisal is a significant predictor for the extent of cortisol stress response (Gaab, Rohleder, Nater, & Ehlert, 2005).

Interestingly the effect of CBSM persists. Four months after receiving CBSM, healthy women and men displayed a reduced cortisol response in an acute stress situation (Hammerfald et al., 2006).

A number of CBSM interventions with patients infected with HIV were conducted, leading to a significant reduction in psychosocial distress and has been shown to enhance coping and immune functioning (Antoni et al., 2002; Antoni, Cruess, Cruess, Kumar et al., 2000; Chesney, Folkman, & Chambers, 1996; D. G. Cruess, M. H. Antoni, N. Schneiderman et al., 2000; Lutgendorf et al., 1997).

The question if CBSM might improve health via modification of biological processes will be discussed in the next part.

2.3.2.3 CBSM for seropositve patients and their physiological outcomes

A number of pathways were discussed through which psychological interventions might plausibly influence disease outcomes (J. E. Bower & Segerstrom, 2004). The following chapter specifies the potential effects of group interventions on the physical health of HIV infected individuals, especially their possible impact on biological or medical outcomes. A particular focus of interest was whether group intervention might affect disease progression and some of the biological processes thought to influence these endpoints (see chapter 2.2.3), answering the question of "The Great Debate" "Do behavioural interventions have a direct influence on the course of diseases?", especially in HIV.

Some evidence showed that group intervention might have a direct impact on relevant biological processes such as immune activity (e.g. natural killer cell function, preservation of T helper cells) and neuroendocrine function (e.g. cortisol-induced changes), via alterations in HPA axis or SAMS activity (A. C. Sherman, Leszcz et al., 2004).

Changes in psychosocial outcomes via behavioural level (e.g., changes in health practices, interactions with medical providers, adherence to demanding treatment regimens) and their possible impact on biological or medical outcomes are not mentioned here (for review see (A. C. Sherman, Mosier et al., 2004). It should be kept in mind that a variety of behavioural factors have an impact on disease outcomes (Williams, Schneiderman, Relman, & Angell, 2002), however there has been little research on whether or how behavioural interact which physiological mechanisms (Freedland, Miller, & Sheps, 2006).

The effects on biological outcomes of group interventions are inconsistent, but some studies found changes in an array of cellular immune factors (changes in antibody titers to latent herpes viruses (HSV-2)) and neuroendocrine (changes in cortisol and in cortisol/DHEA-S ratio) parameters among patients with HIV.

A lot of studies performed at the research centre at the University of Miami, focused on gay men who had progressed from asymptomatic to symptomatic HIV infection. Patients of this research group were screened to eliminate confounding influences on immune and endocrine activity and then were stratified for level of antiviral medication use and randomized to a 10-week cognitive-behavioural group or to a wait-list control condition.

The documentation is not clear, leading to the assumption that some of these reports may reflect overlapping cohorts (A. C. Sherman, Leszcz et al., 2004), e.g. Antoni (2005) mentioned in his article that his current data was published with the same set of data from a prior study (Antoni et al., 2005).

The effect of stress management on psychoneuroimmunology (PNI)-based outcomes in persons with HIV could be demonstrated in a series of studies.

Antoni (2000) found that symptomatic HIV infected gay men who were assigned to multimodal CBSM showed a significantly reduced 24-hour urinary free cortisol output compared to controls

(Antoni, Cruess, Cruess, Kumar et al., 2000). Similarly Goodkin (1998) reported reductions in plasma cortisol in HIV positive men participating in a bereavement support group. Mean plasma cortisol level stabilized initially postintervention and then decreased at 6 months, while the mean plasma cortisol level of control subjects increased over 6 month (Goodkin et al., 1998).

Furthermore during relaxation training with symptomatic HIV positive gay men participating in a 10-week, group-based CBSM training, pre-session salivary cortisol levels decreased over the 10-week period (D. G. Cruess, M. H. Antoni, M. Kumar et al., 2000). The authors discussed that possible changes in cognitive coping strategies or increased supportive elements of the group may be contributing to changes in cortisol and mood.

A cortisol reduction after CBSM was also found in patients with early stage breast cancer. Cruess (2000) revealed that participants showed increased benefit finding and reduced serum cortisol levels, whereas control subjects experienced neither change (D. G. Cruess, M. H. Antoni, B. A. McGregor et al., 2000). In contrast, HIV seropositive patients (D. G. Cruess, M. H. Antoni, N. Schneiderman et al., 2000) could not demonstrate significant differences in cortisol between the CBSM and control groups. The CBSM and control group showed no significant change in cortisol from pre- to post-intervention. However, men in the CBSM intervention had a significantly increased testosterone level relative to the control patients but there was no association between observed change in free testosterone levels and cortisol levels during the study period (D. G. Cruess, M. H. Antoni, N. Schneiderman et al., 2000).

In a prior investigation, Cruess (1999) observed that CBSM buffers decreases in DHEA-S and increases in the cortisol/DHEA-S ratio, potential surrogate adrenal markers of HIV disease progression (Cruess et al., 1999). As well as with his later results, Cruess found no changes in cortisol, suggesting that the effect seems to be mainly driven by reductions in DHEA-S levels among the control subjects across the 10-week study period (Cruess et al., 1999). However if DHEA-S is acting as a cortisol antagonist (Wolf & Kirschbaum, 1999) and maintains cortisol homeostasis, an inadequate DHEA-S level might be a factor for disease progression (Hechter et al., 1997).

Another study group could not detect any differences in cortisol levels among CBSM participants, social support group (SSG) and waiting-listed control groups at any time. However there was a marginally higher DHEA level in the CBSM group compared to the SSG and wait group, which might reflect a trend toward the inversion of the cortisol/DHEA ratio (McCain et al., 2003). In contrast to the other examinations that focused exclusively on patients without AIDS, 30.5% of the total sample was classified as having AIDS.

Only one study focused on the effect of stress management intervention on parameters of the sympathetic-adrenal system in HIV seropositive subjects. The CBSM group revealed a significantly lower posttreatment level of NE compared to the wait-list control but no group differences in E values at posttreatment were proven (Antoni, Cruess, Cruess, Lutgendorf et al., 2000).

These results are important, as they provide evidence that CBSM can slightly have a direct influence on endocrine parameters of the two stress axes (HHNA and SAMS). Both are known to have an in-

cremental influence on the immune system (see chapter above), which might be relevant for health outcome and disease progression in HIV.

Endocrine changes due to CBSM are often associated with a decrease in distress; respectively psychological effects are accompanied by endocrine modulations that might mediate immunologic changes.
HIV infected gay men assigned to CBSM courses showed a greater reduction in 24-hour urinary free cortisol and in parallel showed lower posttreatment levels of depression (Antoni, Cruess, Cruess, Lutgendorf et al., 2000).
Furthermore a decrease in pre-session salivary cortisol levels during relaxation training was related to decreases in global measures of total mood disturbance and anxious mood (D. G. Cruess, M. H. Antoni, M. Kumar et al., 2000). Even the effect of CBSM on cortisol in woman with early stage breast cancer was mediated by increases in benefit finding (D. G. Cruess, M. H. Antoni, B. A. McGregor et al., 2000). Furthermore the decline in free testosterone in HIV seropositive subjects assigned to CBSM was inversely related to changes in distress states over time, independent of any changes in cortisol level (D. G. Cruess, M. H. Antoni, N. Schneiderman et al., 2000).
In addition changes in the cortisol/DHEA-S ratio were significant and positively related to changes in total mood disturbance and perceived stress over time, although no significant relationship was observed between the psychological measures and DHEAS-S levels alone (Cruess et al., 1999).
Moreover pre-post changes in NE were uniquely associated with pre-post changes in anxiety (CBSM participants showed a significantly lower posttreatment anxiety than their control-group counterpart) (Antoni, Cruess, Cruess, Lutgendorf et al., 2000).

Interestingly there is some evidence for the hypothesis that psychological interventions can modulate the immune response in humans. Stress management shows scattered evidence of success (Miller & Cohen, 2001).
In a pioneering study, Antoni demonstrated that HIV-1 seropositive men revealed increases in CD4+ T helper cells and NK cells (CD56), as well as a greater lymphoproliferative response to PHA after CBSM (Stress management and relaxation components) relative to their control group counterparts (Antoni, Baggett et al., 1991).
A further examination showed that over the course of behavioural intervention (CMSB and aerobic exercise) HIV-1 seropositive and seronegative subjects had a significant decrease in Epstein-Barr virus viral capsid antigen (EBV-VCA) and HHV-6 antibody titers, suggesting improved immunologic surveillance (Esterling et al., 1992). Both are indirect markers of antiviral immunity, as studies indicate that co-infection with EBV or HHV-6 may accelerate HIV disease progression (Carrico et al., 2005). Probably EBV infected B-lymphocytes serve as a reservoir for HIV and might present a cofactor in the development of AIDS, through expression of the CD4 receptor on EBV infected B-lymphocytes. The

co-infection of CD4+ cells by HHV-6 and HIV can intensify HIV induced lymphocytolysis (Esterling et al., 1992).

Furthermore, relative to control patients, participants in the cognitive-behavioural group revealed decreased Herpes simplex virus type 2 immunoglobulin G antibody titers. However in this investigation there were no changes in CD4+ or CD8+ cell count or antibody titers to HSV-1 (Lutgendorf et al., 1997). Herpes viruses are cofactors in the pathogenesis of AIDS, as an increasing rate of HSV reactivation is linked to immunosupression such as decreasing CD4+ cell count (Celum, 2004).

Carrico (2005) found no significant differences in HSV-2 and HHV-6 antibodies over a period of 12 months in HIV infected gay men between the CBSM and control group. However they detected a sustained effect over 6 to 12 month of CBSM on EBV-VCA (Carrico et al., 2005). Whereas the CBSM participants experienced no change, the control group displayed a significant increase in EBV-VCA. Antoni (2000) found a significantly increased number of T-cytotocic/suppressor (CD3+, CD8+) lymphocytes 6 to 12 months later in those assigned to CBSM which is seen as evidence that CBSM buffers the longer term decline in T cytotoxic/suppressor cells in HIV infected persons (Antoni, Cruess, Cruess, Lutgendorf et al., 2000). A following study of this group revealed that HIV positive men participating in a 10-week CBSM intervention showed increased signs of immune system reconstitution (greater number of transitional naïve T cells ($CD4^{+}CD45RA^{+,}$ $CD4CD29^{+}$) over a 6-12 month follow-up than the control group, independent of the initial number of naïve T cells and HIV virus load (Antoni et al., 2002). However reconstitution of naïve T cells has not yet been replicated by other research teams. While the participants receiving stress management showed a small increase over this period, the control subjects showed more than a 25% decline.

In a current study Antoni (2006) demonstrated in a subsample of HIV positive patients with detectable viral load at study entry, that men in CBSM + MAT (medication adherence training) displayed a significant reduction in HIV viral load during the 15 months, whereas HIV positive patients assigned to MAT only displayed no change at all (Antoni et al., 2006).

Only one other research team has also examined immune changes in HIV infected patients. In a bereavement support group, the participants exhibited a stable CD4+ cell count over 6 months in contrast to a decrease among control patients and a reduction in viral load following intervention. However there was no statistically significant effect on the CD4/CD8 ratio or on the CD8+ cell count (Goodkin et al., 2001; Goodkin et al., 1998).

Other investigations could not detect such definite results. There were no differences in lymphocyte numbers and function between HIV infected gay men participating in a stress management training compared to those in a wait list control group (Coates, McKusick, Kuno, & Stites, 1989).

Mulder (1995) conclude that the psychosocial intervention programs (cognitive-behavioural group therapy or an experiential group therapy program) with asymptomatic HIV infected homosexual men did not cause changes in CD4+ cell decline or T cell proliferative responses to anti-CD3 monoclonal

antibodies. However he described that decreases in distress were related to increases in CD4+ cell counts over the course of the 2-year follow-up (C. L. Mulder, Antoni, Emmelkamp et al., 1995).
A subgroup of HIV patients assigned to a social support group revealed a significant reduction of cytotoxic NK cells, however the CBSM group showed no decline in this parameter. Moreover no additional immune changes (viral load, lymphocytes, cytokines) were detectable in the CBSM group (McCain et al., 2003).
Other research groups were also unable to detect any significant alterations in immune measures, including CD4+ count (Cleary et al., 1995; McCain, Zeller, Cella, Urbanski, & Novak, 1996; Nicholas & Webster, 1996).

The studies also show that the effects of CBSM on changes in immune functioning in HIV seropositive persons are linked to changes in mood.
Beside the reduction of HSV-2 immunoglobulin G (IgG) antibody titers, the CBSM intervention significantly decreased self-reported dysphoria, anxiety and total distress. A decrease in dysphoria significantly predicted lower HSV-2 antibody titers by the end of the 10-week period (Lutgendorf et al., 1997). Significant decrease in HSV-2 IgG antibody titer in HIV seropositive subjects assigned to CBSM was partially explained by improved social support (S. Cruess et al., 2000).
Furthermore anxiety related decrease in NE during CBSM mediates its effects on immune status up to 1 year after intervention (Antoni, Cruess, Cruess, Lutgendorf et al., 2000). Moreover Antoni (2006) demonstrated that a significant reduction in depression over 10 weeks of CBSM+MAT training for HIV positive men with detectable viral load was associated with a decrease in HIV viral load over the 15-month follow-up period (Antoni et al., 2006). Ironson (1994) showed that distress at the time of diagnosis, denial and low adherence during intervention were significant predictors of 2-year disease progression. Changes in denial were significantly correlated with immune status 1 year later (Ironson et al., 1994). Furthermore the reduction in depressive mood swings during intervention has been shown to predict slower rates of T-helper-inducer cell (CD3+CD4+) decline and clinical disease progression over a 2-year period. Greater adherence to the use of stress management techniques was related to a delayed progression to AIDS over a 2-year period among HIV+ men. A current study indicates that the buffering effect of the CBSM intervention over 6 to 12 month on EBV-VCA was not significantly related to changes in dysphoria, social support and lymphocyte population (CD4+, CD8+ and CD4+/CD8+ ratio) (Carrico et al., 2005).

Beside the modulation of certain immune system components in persons with HIV, alterations in the HPA axis or SAMS hormones may occur in parallel, which are related to down-regulation of immune system components relevant to HIV.
Cruess (2000) demonstrated that a decrease in cortisol/DHEA-S ratio levels in patients enrolled in the CBSM group were associated with decreases in IgG antibody titer to HSV-2 during the period of in-

tervention (S. Cruess et al., 2000). Men in the control condition demonstrated no changes in both parameters and a greater decrease in NE output. An increased frequency of relaxation practice at home during the 10-week CBSM intervention period predicted higher CD3+, CD8+ cell counts at follow-up (Antoni, Cruess, Cruess, Lutgendorf et al., 2000).

Little is know about the possible neuroendocrine changes occurring with these intervention-associated improvements in mood that might influence important immune parameter e.g. the reconstitution of naïve CD4+ T-cells
One single study Antoni (2005) showed that a greater reduction in cortisol and depressed mood during the CBSM training appeared to mediate, in part, effects of the intervention on transitional naïve T cells, an indicator for immune system reconstitution, over 6 to 12 months follow-up period in patients with HIV(Antoni et al., 2005) .

There are further HIV/PNI intervention studies to date (for review see (Robinson, Mathews, & Witek-Janusek, 2000) which are not exclusively focussed on stress management techniques, such as massage therapy (Diego et al., 2001; Ironson et al., 1996), aerobic exercise (for review see (Nixon, O'Brien, Glazier, & Tynan, 2005), mindfulness-based stress reduction (MBSR) (Robinson, Mathews, & Witek-Janusek, 2003) or relaxation training which might have an influence on PNI outcomes.

However one principle problem is, that the number and kind of techniques used in stress management intervention are variable or were inconsistently labelled and often poorly described. Even CBSM strategies are rarely laid out in standardized treatment manuals. Therefore comparisons of stress management outcome studies are not meaningful at this time (Ong, Linden, & Young, 2004).
It is important to note, that we know very little about the effects of CBSM intervention techniques on HIV disease progression and it is premature to conclude that CBSM offers clinical health benefits for HIV infected persons (Antoni et al., 2005). A meta-analysis by Cohen (1996) revealed that stress management intervention shows no evidence of reliably altering immune outcomes (missing variety of enumerative or functional outcomes that are known to decline with stressful experience) (S. Cohen & Herbert, 1996) and very few HIV studies have examined potential links between group intervention and mortality or progression through clinical stages of diseases (A. C. Sherman, Leszcz et al., 2004).
Even after “The Great Debate” about the clinical evidence that psychological intervention can directly change the course of serious organic diseases (Relman & Angell, 2002), the investigation of HIV is still weak and strong evidence is still missing. Moreover the clinical relevance of immune activity or cortisol changes in HIV patients is somewhat ambiguous.
The studies carried out often have a number of weaknesses, e.g. small sample (and therefore limited power statistical analyses), subsample or preselection of patients (e.g. early stage of HIV disease or only gay men and therefore only a limited transferability to other HIV infected groups) and mostly

short follow-up periods (no delayed effects are detectable). In addition, it is unclear to what extent intervention effect can be transferred to the HAART era, as most data was collected prior to using HAART.

Beside those limitations, investigations of the role of psychological factors of AIDS pose difficult methodological challenges e.g. the time of infection is usually difficult to determine and the effect of medication is difficult to determine (S. Cohen & Herbert, 1996).

Although the studies revealed some limitations, there is still a general consensus on the positive effects of a number of interventions on psychological and physiological parameters in HIV infected persons.

These results indicate that behavioural intervention might have a beneficial salutary immunological and clinical health effect among HIV-infected persons.

2.3.2.4 Theoretical framework and study aim

The conceptual implications of our study are based on the psychobiological framework of stress related influences in HIV (adapted from (Steptoe, 1991) (see Figure 2).

According to transactional theory (see chapter 2.3.2.1) the model assumes, that psychobiological stress occurs if an imbalance between psychosocial demands (depending on intensity, duration, complexity novelty, predictability and potential controllability of the stimulation) and resources of the person (prior experience to stress, personal qualities, social network and support, coping strategies) exist (Steptoe, 1991).

In addition Steptoe distinguished two major pathways through which psychobiological stress responses may influence health, respectively disease progression: The indirect cognitive behavioural and the direct psychophysiological pathway.

Psychosocial stressors influence health outcome via the indirect pathway, e.g. through health related behaviour and practices (alcohol and nicotine consumption etc.), symptom appraisal and expressing behaviour independently of any direct action of stress on the physiological system, whereas the direct pathway mediates the stress-illness relationship through psychophysiological responses, e.g. stress-induced changes in autonomic, endocrine and immune function. Those changes might be implicated in aetiology, maintenance and progression of disease process.

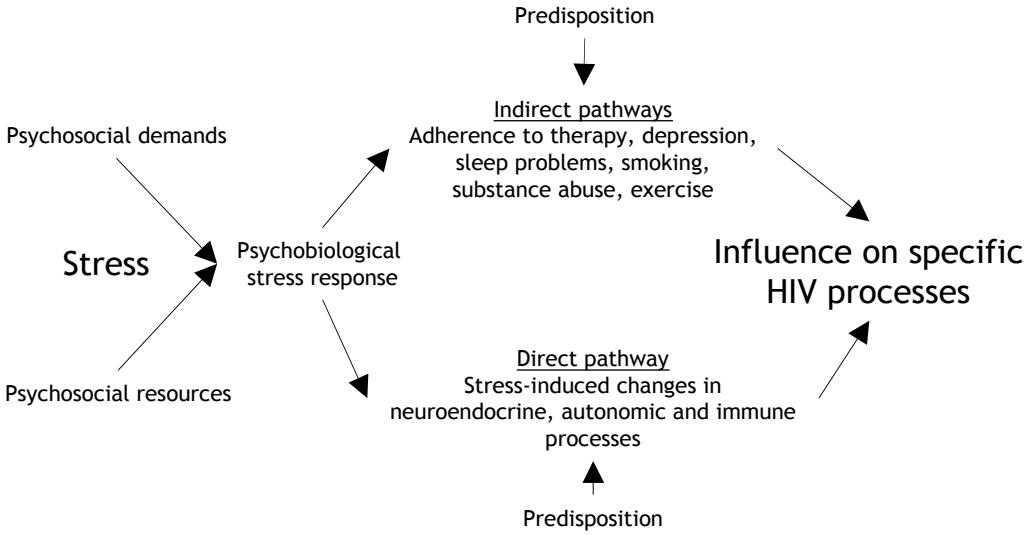

Fig. 2: Psychobiological framework of stress-related influences on disease processes in HIV (adapted from Steptoe 1991)

The aim of this dissertation is to verify if CBSM can perhaps modify direct mediators of health outcomes in HIV disease such as endocrine stress parameters of the HHNA or the SAMS.

We will especially be investigating the direct pathway through which the psychobiological stress response affects HIV disease, supposing that CBSM influences the psychoneuroendocrine and autonomic stress-reaction, which might consequently influence HIV disease markers.

Therefore we examine the stress-answer of HIV patients in an acute stress situation (Trier social stress test; (Kirschbaum et al., 1993) and we are assuming that HIV seropositive persons assigned to CBSM have a decreased stress response under acute stress compared to those not assigned to CBSM.

The investigation is one basic step to prove that disease outcomes are mediated by direct, physiological mechanisms, which was postulated during the “Great debate”, to answer the question whether psychological and social intervention can directly change the course of serious organic disease (Freedland et al., 2006).

3 Psychoneuroendocrine stress reactions in HIV infected patients after cognitive behavioural stress management training

3.1 Introduction

Stress is an important aspect of disease progression, especially in chronic diseases like HIV. Therefore cognitive behavioural stress-management-training (CBSM) has become a key therapeutic intervention in stress reduction among the HIV clinical population.

Stress is defined as a state of threatened internal homeostasis eliciting a coordinated stress response that involves the activation of the HPA-axis and the immune system (Chrousos, 1998). Recent studies suggest that chronic psychological stress alters the neuroendocrine-immune relationship in HIV, which in consequence might influence HIV progression (S. W. Cole & Kemeny, 1997; Leserman, 2003b). A number of studies have demonstrated that stressful life experiences have a profound impact on the disease status in HIV infected persons (Evans et al., 1995; Evans et al., 1997; Goodkin et al., 1998; Goodkin et al., 1996; Howland et al., 2000; Ironson et al., 1994; Kimerling et al., 1999; Leserman et al., 1999; Leserman et al., 2000; Leserman et al., 2002; Leserman et al., 1997). Severe stress and also emotional distress were associated with enhanced markers of disease progression and consequently with an increased risk of AIDS (e.g. CD4+, CD8+, HIV clinical symptoms) (Evans et al., 1995; Ickovics et al., 2001; Leserman et al., 1999; Leserman et al., 2000; Leserman et al., 2002).

The dysregulation of the HPA axis might be a potential mechanism underlying the adverse effect of stress on disease progression and mortality in HIV.

Several studies have indicated that higher levels of cortisol are linked to a greater risk of disease progression (Antoni, Baggett et al., 1991; Goodkin et al., 1996; Leserman et al., 2000; Leserman et al., 2002; Petitto et al., 2000). Under conditions of stress, cortisol has been associated with a decrease in lymphocyte function and reduced mitogen response (Antoni, Baggett et al., 1991; Goodkin et al., 1996). Furthermore, stress induced high cortisol activity was related to a lower number of killer lymphocytes (Petitto et al., 2000) and cortisol predicted independently of psychosocial variables the progression to AIDS (Leserman et al., 2000).

In addition, a complex alteration of adrenal steroid production due to the HIV infection itself was observed in patients. Subclinical endocrine abnormalities of the adrenal gland are already common at an early stage of HIV infection and become clinically manifest as a significant adrenal insufficiency at later stages of the disease (Freda & Bilezikian, 1999), which is mainly characterized by an elevated cortisol level (Christeff et al., 1992; Villette et al., 1990).

Opportunistic infections, medication and antiretroviral therapy might be potential etiologies of endocrine disturbances in HIV infection (Eledrisi & Verghese, 2001), e.g. antiretroviral drug regimens with protease inhibitors (PI) have an influence on parameter of the HPA (Christeff et al., 2000; Collazos et al., 2004; Collazos et al., 2003). The disease may also directly influence HPA axis activity. For example the gp120 envelope protein has been shown to influence the HPA axis centrally via CRF synthesis

modulation (Pozzoli et al., 2001) and the HIV-1 accessory protein Vpr could act as a potent co-activator on glucocorticoid receptors (GR) in lymphoid cell lines (Kino et al., 1999), both lead to an increased cortisol level.

Thus, changes of the HPA axis, respectively the cortisol level occur during psychosocial and infectious stress and have been linked to disease progression, which emphasises the importance of cortisol as a mediating mechanism.

The influence of cortisol has been discussed controversially and so far little clinical evidence exists. Beside increased viral replication (Markham et al., 1986) and inhibition of NK cell activity due to GC (M. P. Nair & Schwartz, 1995), changes in cytokine patterns from T_h1 to T_h2 cytokines have been proposed to be involved in disease development. T_h2 cytokine profile could be demonstrated in patients with HIV (S. A. Klein et al., 1997; Sindhu et al., 2006) and was related to disease progression (Clerici, Villa et al., 1994). The same modification of cytokine patterns has also been proposed by a chronic stress model, which assumes that stress might simultaneously enhance and suppress immune response by altering the cytokine secretion with a shift toward T_h2 cytokines, which might in consequence increase the vulnerability for immune dysregulation (Agarwal & Marshall, 1998). This indicates that HIV and stress may take the same "physiological highways", which could explain faster disease progression in HIV during stress and underline the significance of GC action. Besides the effect of cortisol via cytokines, cortisol might further be responsible for the decline in DHEA and increased cortisol/DHEA ratio in HIV infected persons, which has also been associated with reduced immune function and was viewed as an independent predictor for disease progression (Christeff et al., 1997; de la Torre et al., 1997; S. Grinspoon et al., 2001). Hence dysregulation of the HPA axis, respectively elevated cortisol levels due to infectious disease and/or psychosocial stress, may potentially affect the course the disease.

Some studies have demonstrated that the way of coping with stress may change the course of HIV-1 infection. Persons, who cope with stressful events by finding meaning or using active coping, have reduced HIV symptoms and a delayed clinical progression (J. E. Bower et al., 1998; Ironson et al., 1994; Leserman et al., 2000; C. L. Mulder, Antoni, Duivenvoorden et al., 1995; Solano et al., 1993; Vassend et al., 1997). Interestingly, the extent of cortisol release might also be linked to the experience or anticipation of stress (Dickerson & Kemeny, 2004; Gaab et al., 2005; Smyth et al., 1998).

Cognitive-behavioural stress management (CBSM) training tends to reduce perceived stress by improving stress related cognitive coping strategies and has been used in numerous investigations in HIV. Some evidence exists that CBSM might have a direct impact on HIV relevant processes such as neuroendocrine function. A decreased cortisol level (Antoni, Cruess, Cruess, Kumar et al., 2000; Goodkin et al., 1998) and a decreased cortisol/DHEA ratio (Cruess et al., 1999) have been found in HIV patients assigned to CBSM. Moreover, neuroendocrine changes are associated with a decrease in perceived stress or distress (Antoni, Cruess, Cruess, Kumar et al., 2000; Cruess et al., 1999; D. G. Cruess, M. H. Antoni, N. Schneiderman et al., 2000). Furthermore, alterations of the HPA axis

through CBSM were related to modulation of immune components relevant to disease progression (Cruess et al., 1999).

However, previous clinical studies in HIV have never evaluated the effect of CBSM training under stress conditions, parameters were always recorded during a resting phase. In healthy subjects it has already been demonstrated that CBSM attenuates stress reactivity during an acute stress test, influenced only by differences in cognitive appraisal (Gaab et al., 2003; Hammerfald et al., 2006). Additionally, all studies were performed in the pre-HAART era and the findings were not transferable to persons using highly active antiretroviral therapies (HAART).

Therefore, the main purpose of this investigation was to evaluate the effect of a group-based CBSM training on the acute neuroendocrine stress response in HIV infected patients under HAART. Our intention was to answer the question whether CBSM training can influence HPA axis activity, a possible direct endocrine mediator of health outcomes in HIV disease.

3.2 Methods

3.2.1 Subjects

HIV seropositive patients (men and women) were recruited for study participation from the SHCS-Centre (Swiss HIV Cohort Study) between December 2003 and July 2004. Participants were between the age of 18 and 60, were members of the SHCS and had been taking HAART medication at least 3 months prior to study entry. Exclusion criteria were a CD4+ lymphocyte count < 100, active opportunistic infections, the initiation of a new psychotherapy within the past 3 months and patients not fluent in German.

To ensure that all participants would be appropriate for group CBSM, we also excluded subjects meeting criteria for mental and behavioural disorders due to psychoactive substance abuse (F10-F19) or major psychiatric diagnosis [i.e., schizophrenia, schizotypal and delusional disorders (F20-F29), manic episode (F30.0), bipolar affective disorder (F31.0), severe depressive episode with or without psychotic symptoms (F32.2, F32.3) or personality disorders (i.e. paranoid personality disorder (F60.0) or schizoid personality disorders (F60.1))]. We used a standardized and structured computer-aided version of the Munich Composite International Diagnostic Interview (DIA-X/M-CIDI) (Wittchen & Pfister, 1997), and the SCID II (Wittchen, Zaudig, & Fydrich, 1997) for psychological screening.

3.2.2 Study design

The study was a randomized controlled trial study (treatment vs. waiting list control condition) with repeated assessment of dependent variables (pre- and post training, 6 and 12 months follow-up evaluation). It was conducted in four German-speaking Swiss HIV centres (Basel, Bern, St. Gallen, Zürich), representing the German-speaking area of Switzerland.

During the recruitment period 1157 patients were eligible for screening (see fig. 3). Among those, 102 enrolled in the study and were randomly assigned to either the 12-week CBSM intervention (N = 53)

or to a waiting list control condition (N = 49; subjects received the CBSM-intervention at the end of the study). Of the remaining eligible patients, 1047 actively refused participating in the study.

Randomization, performed centrally with the use of sealed envelopes containing allocations from a computer-generated table of random numbers, was stratified according to the centre (4) and the CD4+ cell count <200/≥200. A 4:4 ratio of randomization (intervention group: control group) was used. Assignment to study conditions was conducted subsequent to screening.

Among the 102 enrolled subjects, 23 subjects (18 experimental, 5 control) withdrew from the study prior to completion of the intervention, leaving 75 patients to complete the posttreatment assessment. Of those, a total of 71 participants underwent the Trier Social Stress Test, which took place one month after termination of the CBSM, subsequent to post assessment.

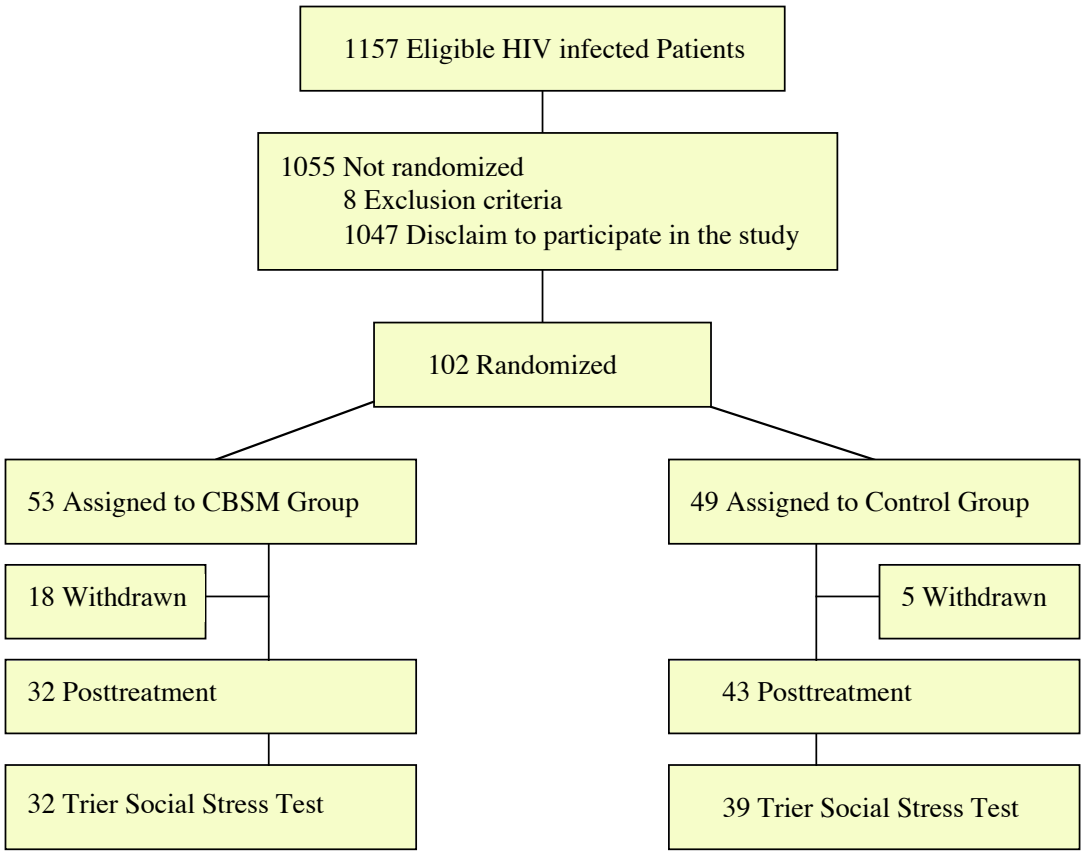

Fig. 3: Flow Diagram of Participant Screening, Randomization, Posttreatment and Trier Social Stress Test

3.2.3 Procedure

3.2.3.1 Cognitive behavioural stress management training

Cognitive behavioural stress management training (CBSM) is based on the principles of the stress inoculation training developed by Meichenbaum (Meichenbaum & Novaco, 1985) and modified according to F. H. Kanfer`s self management, K. Grawe`s psychological psychotherapy and the HIV group program developed within the scope of the EUROVIHTA-project (Escobar Pinzón, 2000; Grawe, 2002; Kanfer et al., 1996).

CBSM training was a 2-hour, group-based (4-10 subjects per group) intervention, taking place weekly over a 12-week period. The intervention consisted of cognitive-behavioural stress-reducing techniques (cognitive restructuring, problem solving, self-instruction), assertiveness training, satisfaction of personal needs, strategies for using social support and self-management training. These techniques were practiced along with 10 themes (vertical training modules). Five themes were fixed (1. stress, 2. depression, 3. social support, 4. stigmatization, 5. influence of HIV on personal aims) and five themes were variable (a. medications and their side effects, b. dealing with crisis, sexuality and partnership, c. stress at work or unemployment, d. social competence, e. health behaviour and well being, f. fatigue, g. anxiety, h. death) and were chosen by the group members after the first meeting (introduction session). Additionally, each session included group dynamics and progressive muscle relaxation (horizontal training modules).

Each group session had the same schedule, starting with a horizontal training module (group dynamics), followed by a vertical training module (introduction to the current theme) and, after a short break (10 mins.), followed by another horizontal training module (progressive muscle relaxation), another vertical module (training according to the current theme) and eventually ending with a horizontal training module (group dynamics). At the end of each group therapy session, participants were given homework permitting them to practise the learned techniques in real life.

During each session, participants received a summary of the practised theme and the stress-reducing technique, as well as flash cards briefly describing each technique. Each group was managed by two postdoctoral psychotherapists in training (always one male and one female psychotherapist) according to a training manual.

3.2.3.2 Psychosocial stress test

The Trier social stress test (TSST) consists of an anticipation period (10 mins.) and a test period (a five-minute job application speech and a five-minute unprepared mental arithmetic task performed out loud in front of an audience and a camera).

The TSST has been found to induce profound cortisol, ACTH and cardiovascular responses in 70-80% of subjects (Kirschbaum et al., 1993) and to provoke the most robust physiological stress responses compared to other laboratory stress tasks (Dickerson and Kemeny, 2002).

After arrival at the laboratory, an intravenous catheter was inserted into the subject’s forearm to allow

for periodic collection of blood samples. After a resting period of 30 minutes, a baseline blood and saliva samples were taken. The subjects were then guided to the TSST room, where they were introduced to the task they would have to perform subsequently (2 mins.). They then returned to a different room, where they were given 10 minutes to prepare and 5 minutes to complete a questionnaire designed to assess cognitive appraisal processes (Primary appraisal secondary appraisal scale, PASA; (Gaab et al., 2005). After spending the preparation period in solitude, a second blood and saliva sample was taken (-11 mins.). Then, the subjects started the test period by taking part in a simulated job interview. After five minutes, the task changed to performing serial subtractions of 17 starting at the number 2023. Whenever the subjects made a mistake, they were required to restart at the number 2023. Immediately after the 10 minutes test period, the subjects were guided out of the room and a third blood and saliva sample was taken (+1 min.). Then, the subjects completed a second set of questionnaires (Skala zur Erfassung des Bewältigungsverhaltens (SEBV; (Fillip & Ferring, 1989); Ways of coping checklist; Folkman & Lazarus, 1980) to assess coping behaviour. Subsequently, they were requested to complete a form concerning current substance abuse and medication other than antiretroviral therapy. Further blood and saliva samples were collected at +10 mins., +20 mins., +30 mins., +45 mins. and +60 minutes after the test period. Eventually, the participants were debriefed. The TSST was performed between 13.00 and 19.00 h.

3.2.4 Outcome measures

3.2.4.1 Control variables

At pre and post training, potentially confounding outcome parameters such as medical characteristics, antiretroviral medications and medical history were assessed at the Swiss HIV centres. Also, demographic variables as well as behavioural and mood data (depression and anxiety; Hospital depression and anxiety scale, HADS-D, Hermann et al., 1995) were collected from patients.

3.2.4.2 Psychometric measures

Anticipatory cognitive appraisal processes in the TSST were assessed with a situation-specific transactional stress questionnaire PASA (Primary appraisal secondary appraisal scale). This questionnaire consists of one tertiary scale “stress index” which is composed of two secondary scales, “primary appraisal (PA)” and “secondary appraisal (SA)” which are respectively composed of four primary subscales: “challenge (PA)” and “perceived threat (PA)”, “self-concept of own competence (SA)” and “control expectancy (SA)”. The PASA scale has a good reliability and validity (Gaab et al., 2005).

To assess the coping behaviour in the TSST, we used the German version of the “Ways of coping checklist” (SEBV: Skala zur Erfassung des Bewältigungsverhaltens). This short version was proven to be adequate in differentiating between emotion-focused (palliative) and problem-focused coping behaviour (Ferring et al. 1989). The SEBV consists of 2 subscales, which are “emotion-focused” (18 items) and “problem-focused” (18 items).

3.2.4.3 Physiological measures

To determine free cortisol, plasma cortisol and plasma ACTH concentrations, saliva and blood samples were collected at -30 and -11 minutes before and +1, +10, +20, +30, +45 and +60 minutes after stress exposure (TSST-test period).

Saliva samples were collected by chewing on a dental cotton log (Salivettes, Sarstedt, Rommelsdorf, German) and were stored at -20°C immediately after collection until the end of the study and thawed before biochemical analysis.

Blood samples were placed on ice and then centrifuged with the plasma pipetted off and stored at –80°C before analyzing the samples.

3.2.5 Biochemical analyses

Saliva cortisol assay

50µl of saliva were used for duplicate radioimmunoassay (RIA) measurements using the scintillation proximity assay (SPA system Amersham-Buchler, Braunschweig, Germany) and tritium labelled cortisol (Amersham-Buchler, Braunschweig, Germany). The sensitivity of the assay was 130.1 nmol/L. The interassay variance was less than 10%.

Plasma cortisol

Plasma cortisol and cortisone was analyzed with high-performance liquid chromatography with UV detection as described in detail elsewhere (Volin, 1995).

ACTH assay

ACTH was measured by enzyme immunoassay (enzyme-linked immunosorbent assay (ELISA)) according to the manufacturer‘s instructions (IBL immuno-biological laboratories, Germany).

Intra- and interassay variability was less than 4.2 and 6.2% (CV% coefficient of variation), respectively.

3.2.6 Statistical analyses

Repeated-measures ANOVA (Analyses of variance) was performed to analyse endocrine data, with “treatment” as grouping variable and “time” as repeated measure factor. All reported results were corrected with the Greenhouse-Geisser procedure where appropriate (violation of sphericity assumption). One-way ANOVA was computed for comparison of areas under the curve (AUC). Areas under the curve were calculated with respect to ground (AUCg = area under all sample) and with respect to increase (AUCi = area under all sample with reference to the first value) for endocrine parameters using the trapezoid formula (Pruessner et al., 2003).

Data was tested for normal distribution and homogeneity of variance using a Kolmogorov-Smirnov and Levene`s test before statistical procedures were applied. In case of non-normal or skewed distri-

bution ln-transformation for endocrine and autonomic parameters, log-transformation for viral parameters (RNA) and square root transformation for immune and psychometric parameters were performed.

The two groups were compared with respect to demographic, behavioural, psychological and medical characteristics using the chi-square-test for categorical data, Mann-Whitney-U-test for ranked data or not normally distributed variables and one-way analysis for continuous data. Descriptive statistics included percentage for categorical data, median and range for ranked data and mean values (+/-SD) for continuous data. Means and standard deviations of untransformed values are presented.

Some data was missing due to equipment problems, difficulties in taking blood samples and failed biochemical analysis so that the analyses are based on 57 subjects for the parameters in ACTH, 56 subjects for the parameters in plasma cortisol and 64 subjects for the parameters in salivary cortisol.

Statistical significance of all analyses was set at .05. All statistical analyses were performed using SPSS version 11.04 for Macintosh.

3.3 Results

3.3.1 Sample characteristics

There were no group differences in gender, age, body mass index, education, income, sexual orientation or nationality between treatment and control group (see table 1). Additionally, no statistical differences in aerobic exercise and current substance abuse were detected. As well, no differences in depression and anxiety score were found at post training evaluation (see table 2). Also, subjects in the treatment group did not differ in medical characteristics at baseline and post assessment, current medication and medical history (see table 3).

Table 1: Demographic variables (n = 71)

	CBSM group (n = 32)	Control group (n = 39)	Statistic
Gender			
Male	30 (93.8%)	34 (87.2%	NS
Female	2 (6.3%)	5 (12.8%)	
Age (years)			
M	44.9	43.4	NS
SD	8.2	8.3	
Body mass index (BMI) (kg/m^2)			
	23.8	23.0	NS
Schooling			
Some high school or less	22 (68.8%)	25 (64.1%)	
High school graduate	3 (9.4%)	10 (25.6%)	
Other	5 (15.6%)	3 (7.7)	
No graduate	2 (6.3)	1 (2.6)	
Vocational Education			
Trade school/some college	3 (9.4%)	5 (12.8%)	
College degree	16 (50%)	20 (51.3%)	
Other	9 (28.1%)	11 (28.2%)	
No apprenticeship	4 (12.5%)	3 (7.7%)	
Income (sfr/yr)			
Less than 3000	6 (18.8%)	5 (13.9%)	
3000-6000	18 (56.3%)	16 (44.4%)	
6000-9000	7 (21.9%)	14 (38.9%)	
Greater than 9000	1 (3.1%)	1 (2.8%)	
Sexual orientation			
Homosexual/bisexual	21 (65.6%)	20 (51.3%)	
Heterosexual	9 (28.2%)	18 (46.2%)	
Bisexual	2 (6.3%)	1 (2.6%)	
Nationality			
Swiss	30 (93.8%)	33 (84.6%)	
Other	2 (6.3%)	6 (15.4%)	

However the sample varied in the use of antiretroviral regimen at post assessment ($\chi 2 = 3.90$; P = 0.05) (see table 3). At the time of the psychosocial stress test, 40.6% of the treatment group were taking protease inhibitors (PI), whereas the waiting list control group showed a greater proportion (65.1%).

Table 2: Behavioural and mood data

	CBSM group (n = 32)	Control group (n = 39)	Statistic
Aerobic exercise			
Yes	14 (43.8%)	23 (59.0%)	NS
No	18 (56.3%)	16 (41.0%)	
Current Substance use			
Tobacco	11 (34.4%)	12 (30.8%)	NS
Cannabis	3 (9.4%)	4 (10.3%)	
Methadone	2 (6.3%)	1 (2.6%)	
HADS[a]			
Depression (post)	4.66 (3.64)	4.23 (3.65)	NS
Anxiety (post)	5.78 (3.32)	5.87 (3.89)	NS

[a] Mean (standard deviation)

Table 3: Medical information

	CBSM group (n = 32)	Control group (n = 39)	Statistic
Immune measures (post)[a]			
CD4 (cells per µl)	523 (324)	526 (218)	NS
CD8 (cells per µl)	930 (430)	824 (321)	NS
Viral load (post)			
Not detectable rna	21 (65.6%)	21 (55.8%)	NS
RNA detectable (> 50 c/ml)	29326 (52486)	26756 (75104)	NS
Illness history			
Nadir CD4[a]	211.22 (156.55)	170.64 (121.04)	NS
CD4 ≤ 200	18 (56.3%)	27 (69.2%)	NS
CDC-C symptoms	11 (34.4%)	10 (25.6%)	NS
Nadir RNA (c/ml)[b]	111095 (1458679)	142412 (1458695)	NS
Number of opportunistic infections[b]	1.20 (10)	1.26 (6)	NS
Antiretroviral regimen			
HAART			
NRTI + PI	9 (28.1%)	20 (51.3%)	
NRTI + NNRTI	10 (31.3%)	5 (12.8%)	
NRTI + NNRTI +PI	4 (12.5%)	4 (10.3%)	
NRTI + ABC	7 (21.9)	6 (15.4%)	
NNRTI + PI	0 (0%)	1 (2.6%)	
Dual therapy	0 (0%)	1 (2.6%)	
Mono therapy	1 (3.1%)	0 (0%)	
No antiretroviral medication	1 (3.1%)	2 (5.1%)	
Use of PI (post)	13 (40.6%)	25 (65.1%)	$\chi^2 = 3.90$; P = .050
Use of NNRTI (post)	15 (46.9%)	11 (28.2%)	NS
Duration of current HAART regime (yr)[a]	7.47 (2.51)	8.00 (2.52)	NS
Further medication at TSST (Same day or day before TSST)			
Heart medication	5 (15.6%)	8 (20.5%)	NS
Medication for the gastrointestinal tract	2 (6.3 %)	5 (12.8%)	NS
Medication for the respiratory tract	1 (3.1%)	3 (7.7%)	NS
Antidepressants	6 (18.8%)	4 (10.3%)	NS
Cholesterol	1 (3.1%)	1 (2.6%)	NS
Analgesics	2 (6.3%)	2 (2.8%)	NS

[a] Mean (standard deviation)

[b] Median (range)

3.3.2 Effect of CBSM training on endocrine stress reaction

Results revealed no significant effect of the CBSM training on the plasma cortisol reaction between treatment and control group.

The TSST provoked a significant plasma cortisol response in all patients ($F_{(1.62/87.68)} = 42.513$; $P < .000$) (see Fig. 4). However two-way ANOVA with repeated measures did not differ between both groups (group by time interaction effect: $F_{(1.62/87.68)} = 0.747$; $P = .451$) and their overall plasma cortisol reponse (group effect: $F_{(1/54)} = 0.364$; $P = .549$) (see table 4). Insignificant effects of ANOVA of the AUCg (group effect: $F_{(1/54)} = 0.516$; $P = .476$) and AUCi (group effect: $F_{(1/54)} = 0.341$; $P = .562$) for plasma cortisol confirmed this result (see table 5).

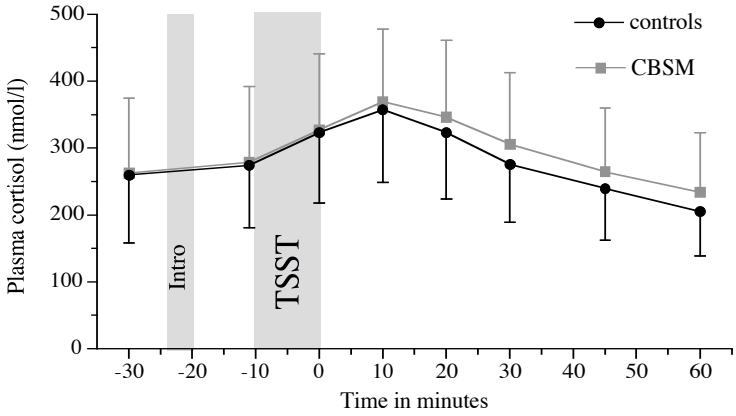

Fig. 4: Plasma cortisol responses in the TSST

Table 4: Results of endocrine response to stress in treatment and control group

	Time effect	Group x time interaction	Group effect
Plasma cortisol	F (1.62/87.68) = 42.513; P < .000	F (1.62/87.68) = 0.747; P = .451	F (1/54) = 0.364; P = .549
Salivary cortisol	F (2.05/126.98) = 16.358; P = .000	F (2.05/126.98) = 0.045; P = .634	F (1/62) = 0.275; P = .602
ACTH	F (3.13/172.22) = 54.633; P < .000	F (3.13/172.22) = .587; P = .632	F (1/55) = 1.060; P = .308

Likewise, there were no differences in the salivary cortisol reaction between patients assigned to CBSM training and the control group (see Fig. 5). In a two-way ANOVA with repeated measures, both groups showed a significant increase in their salivary cortisol response ($F_{(2.05/126.98)}$ = 16.358; P = .000) after stress exposure but the groups did not differ in their salivary stress response over time (group by time interaction effect: $F_{(2.05/126.98)}$ = 0.045; P = .634) and their overall salivary cortisol reponse (group effect: $F_{(1/62)}$ = 0.275; P = .602) (see table 4). Furthermore, results obtained by ANOVA indicated no significant differences in AUCg (group effect: $F_{(1/62)}$ = 0.024; P = .879) and AUGi (group effect: $F_{(1/62)}$ = 1.116; P = .295) in salivary cortisol between the two groups (see table 5).

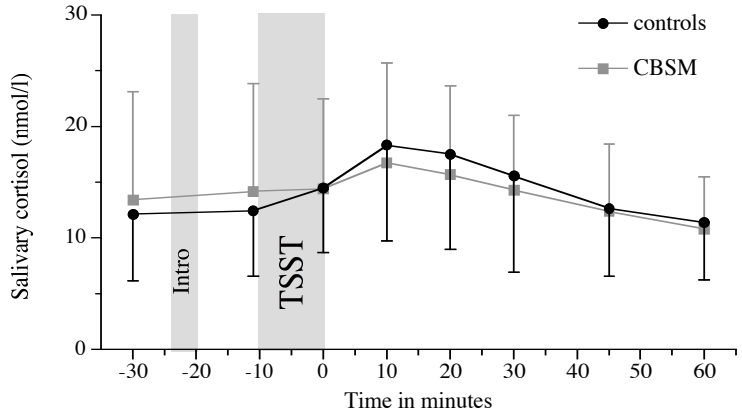

Fig. 5: Salivary cortisol responses in the TSST

Table 5: Group comparisons of the area under the curve parameters

	Parameter	CBSM group [a]	Control group [a]	Statistic
Plasma cortisol (nmo/l)	AUGg	26844 (1488)	25383 (1386)	F (1/54) = 0.516; P = .476
	AUCi	3159 (7298)	1974 (7795)	F (1/54) = 0.341; P = .562
Salivary cortisol (nmo/l)	AUGg	1262 (595)	1283 (473)	F (1/62) = 0.024; P = .879
	AUCi	53.42 (480)	189 (537)	F (1/62) = 1.116; P = .295
ACTH (pg/ml)	AUGg	2579 (1095)	2407 (1197)	F (1/55) = 0.311; P = .579
	AUCi	207 (210)	399 (193)	F (1/55) = 0.451; P = .505

[a] Mean (standard deviation)

Correspondingly a two-way ANOVA with repeated measures revealed a significant ACTH response under acute stress in all patients ($F_{(3.13/172.22)}$ = 54.633; P < .000), but no significant differences in ACTH reaction over time (group by time interaction effect: $F_{(3.13/172.22)}$ = .587; P = .632) and in overall ACTH reaction (group effect: $F_{(1/55)}$ = 1.060; P = .308) were detected between the treatment and the control groups (see table 4, see Fig. 6). Along with these results, the groups did not differ in AUCg (group effect: $F_{(1/55)}$ = 0.311; P = .579) and AUCi of ACTH (group effect: $F_{(1/55)}$ = 0.451; P = .505) (see table 5).

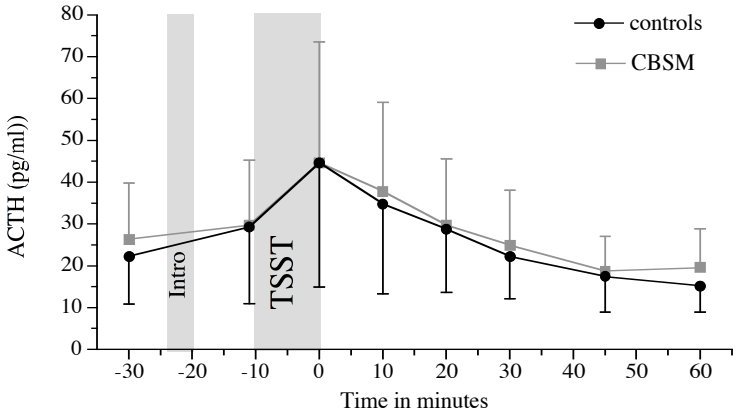

Fig. 6: ACTH responses in the TSST

As reported above (see 3.3.1), groups differed in their use of PI-based regimens and recent studies indicated that PI influenced parameters of the HPA. Therefore PI is a potential moderator of outcome (Kraemer, Frank, & Kupfer, 2006; Kraemer, Wilson, Fairburn, & Agras, 2002). Consequently, PI was treated as a moderator variable. Moderation was tested by hierarchical regression equation as described by Cohen (J. Cohen, Cohen, P., West, S. G., Aiken, L.S., 2003). In case of significant treatment by PI interaction effect, interaction was analysed using simple effect analysis (Baron & Kenny, 1986).

The use of PI-based regimens was no moderation variable of plasma cortisol. We found no significant group by PI interaction effect for the AUCg plasma cortisol reaction. However, results obtained by hierarchical regression analysis showed a significant main effect of PI on AUCg plasma cortisol (PI: ß = .545, t = 2.815; p = .007; $R^2_{adjust.}$= .90, $F_{(3/52)}$ = 2.880, p = .045). Therefore, PI might be called a non-specific predictor of outcome (Kraemer et al., 2002). As shown in figure 7 patients, who took antiretroviral drug regimens with PI showed a higher plasma cortisol response in acute stress situations than patients who took antiretroviral drug regimens without PI.

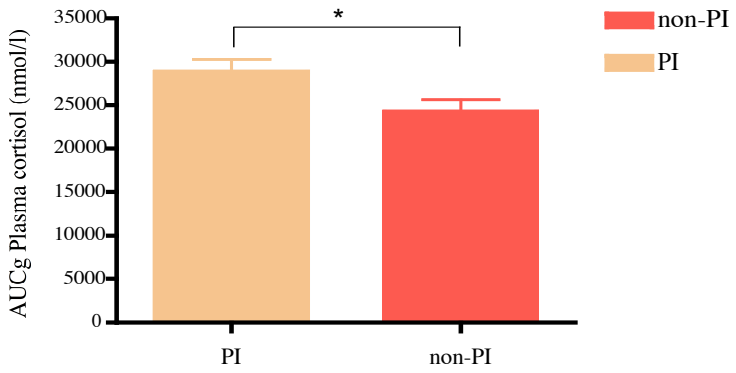

Fig. 7: AUGg plasma cortisol in the TSST for non-PI users compared to PI users

The variable PI did not moderate the causal effect of CBSM on AUCg salivary cortisol response; there was no significant group by PI interaction effect for the AUCg salivary cortisol reaction.

In contrast, the use of PI-based regimens was a moderator variable of ACTH. We detected a significant group by PI interaction for the AUCg ACTH reaction (see table 6). Simple effects of treatment revealed no significant difference between treatment and control groups at the level of non PI-users in the AUCg ACTH response ($F_{(1/54)}$ = 2.56; P = .116), There was, however, a significant difference in the AUCg ACTH response between the CBSM and control groups at the level of PI-users ($F_{(1/54)}$ = 5.91; P = .018), such that the mean for the CBSM group was higher than for the control group (see disordinal interaction fig. 8).

Further, within the treatment group, patients taking antiretroviral drug regimens with PI differed in their ACTH reaction (AUCg ACTH) from those who took antiretroviral drug regimes without PI ($F_{(1/54)}$ = 6.73; P = .012). There was, however, no significant difference between PI-user and non-PI user in the control group ($F_{(1/54)}$ = 2.29; P = .136). Within the treatment group, patients treated with PI-based regimes showed a higher ACTH response than those without PI-based regimens (see fig. 8).

Table 6: Summary of Hierarchical Regression Analysis for Variables Predicting AUCg ACTH (N = 57)

Variable		B	SE B	ß
Step 1				
	Constant	2578.75		
	Group	-170.85	306.36	-.08
Step 2				
	Constant	2487.00		
	Group	-225.30	315.82	-.10
	PI use	238.53	314.65	.11
Step 3				
	Constant	2126.56		
	Group	615.73	414.03	.27
	PI use	1175.69	437.05	.52*
	Group x PI use	-1721.27	592.31	-.72*

Note. R^2 = .01 for Step 1; ΔR^2 = .01 for Step 2 (*p*s = .45) ; ΔR^2 = .14 for Step 3 (*p*s < .05). *p < .05

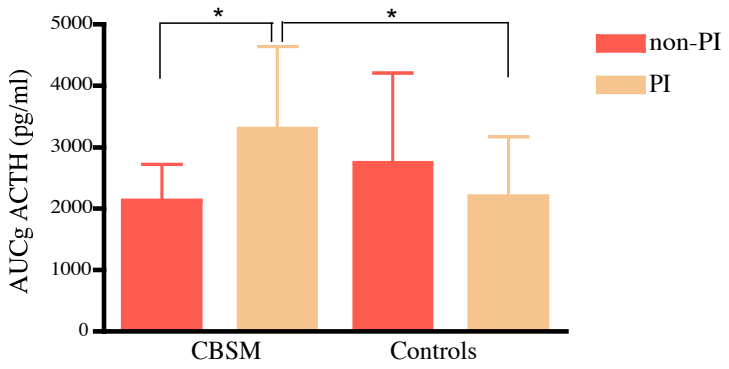

Fig. 8: AUCg ACTH in the TSST; group by PI-treatment interaction

3.3.3 Effect of CBSM training on cognitive appraisal and coping

The groups did not differ in cognitive appraisal and coping style after CBSM training. No group differences were found with respect to secondary PASA scales and the PASA stress index (see table 7). The primary scale "challenge" was significantly lower in the treatment group compared to the control group (group effect: F (1/69) = 3.837; P = .054, r = .23). The other three primary scales (threat, challenge, self-concept) were equal in both groups. We were also unable to detected differences between the two groups in SEBV scales "emotion-focused coping behaviour" and "problem-focused coping behaviour" (see table 8).

Table 7: Comparison of PASA scale between groups

	CBSM group (n = 32)	Control group (n = 39)	Statistic
Primary scales[a]			
Threat	2.8 (0.9)	2.6 (0.9)	F (1/69) = 0.530; P = .469
Challenge	3.9 (0.8)	4.3 (1.0)	F (1/69) = 3.837; P = .054*
Self-concept of own competence	4.2 (0.8)	4.1 (1.0)	F (1/69) = 0.073; P = .788
Control expectancies	4.8 (0.8)	4.8 (0.7)	F (1/69) = 0.001; P = .977
Secondary scales[a]			
Primary appraisal	3.4 (0.7)	3.5 (0.9)	F (1/69) = 0.476; P = .493
Secondary appraisal	4.5 (0.6)	4.5 (0.7)	F (1/69) = 0.030; P = .863
Stress index[a]	-2.2 (2.2)	-1.9 (2.6)	F (1/69) = 0.304; P = .583

[a] Mean (standard deviation)

Table 8: Comparison of SEBV scale between groups

	CBSM group (n = 30)	Control group (n = 35)	Statistic
Emotion focused coping behaviour[a]	2.3 (0.7)	2.5 (0.7)	F (1/63)=0.892; P= .348
Problem focused coping behaviour[a]	3.4 (0.6)	3.4 (0.7)	F (1/63)=0.195; P= .660

[a] Mean (standard deviation)

3.4 Discussion

The present study evaluated the effect of a group-based CBSM training on the hypothalamic pituitary adrenal axis in HIV infected patients undergoing HAART. Therefore, after randomization either to the CBSM treatment group or control group, the patients underwent the Trier social stress test, which took place one month after completion of the CBSM course.

Altogether, the analyses revealed that CBSM had no effect on endocrine stress parameters. ACTH reaction, as well as plasma and salivary cortisol responses, did not differ between treatment and control groups. Both groups did not vary in coping style and cognitive appraisal with exception of the primary scale "challenge" where the treatment group scored less.

However, the sample differed in their use of the antiretroviral PI-regimens. Moderator analysis revealed PI as a nonspecific predictor for the plasma cortisol reaction. Further, we identified PI as a moderator of the CBSM effect on the ACTH reaction in the acute stress situation.

One explanation for the lacking effect of CBSM training on endocrine and cognitive stress responses might be found in the CBSM training itself. In contrast to the studies with healthy subjects (Gaab et al., 2003; Hammerfald et al., 2006), in which the CBSM training was mainly focused on stress-reduction techniques taught over a 2-day period, the CBSM training for HIV infected persons consisted only of one 2-hour session focusing on said techniques. Further, cognitive techniques were practised dealing with other themes like depression, social support or stigmatization to improve personal coping capacity in different areas. The intention was to convey a broad range of coping strategies for several difficult real life situations an HIV patient might encounter. Therefore, the difference in the subscale "challenge" between the two groups might be a result of an attenuated common challenge perception, which could perhaps reflect a generally relaxed attitude during exposure to different life situations, including acute stress situations. It is thus remotely possible that the probability of middle-age men to appraise their problems as challenges (Aldwin, Sutton, Chiara, & Spiro, 1996) is reduced as a result of broadly based applications of cognitive techniques on a variety of life problems. Hence, the limited focus on acute stressful situations during the CBSM course might be a potential reason for the missing treatment effect on endocrine and cognitive results during TSST.

Second, next to the limited practise of stress reduction techniques, differences in demographic characteristics between the healthy CBSM participants of previous studies (Gaab et al., 2003; Hammerfald et al., 2006) and the present HIV population might also explain the absence of changes in coping style or the PASA stress-index and endocrine stress parameters. Mean age was much higher in the HIV seropositive participants (44 years) compared to the healthy adults tested in previous studies (about 23 years).

Age differences in coping strategies have already been detected (Blanchard-Fields & Irion, 1988; Diehl, Coyle, & Labouvie-Vief, 1996; Folkman, Lazarus, Pimley, & Novacek, 1987; Richaud de Minzi & Sacchi, 2005) and might be based on modifications in coping strategies during the individ-

ual's development. This lead us to the assumption that changing the way of coping and appraisal through CBSM training might be more likely in younger adults, who are in a development process of coping behaviour. In contrast, coping behaviour and appraisal might be less flexible in mature adults, as they already have more or less fully developed coping and appraisal strategies.

Age differences in endocrine stress reactivity (Kudielka 2004, Gotthardt 1995) and in basal endocrine stress parameters were also shown (Deuschle 1997). Possibly, the modification of age related changes in the endocrine stress-response via CBSM training is less probable, especially after regressive transformation of the adrenal gland due to the climacteric.

A third possible explanation for the failed results in endocrine reaction might be the influence of antiretroviral treatment, in particularly the use of PI, which were identified as a non-specific predictor for the overall plasma cortisol reaction and as a moderator of the ACTH response.

Until now the impact of antiretroviral treatment on the HPA axis is not fully understood. Numerous side effects, such as LD syndrome, hyperlipidaemia and insulin resistance have been demonstrated with the use of PI (A. Carr, 2000; A. Carr, Samaras, Burton et al., 1998). The biochemical pathogenesis of the side effects has been investigated (A. Carr, Samaras, Chisholm, & Cooper, 1998), but only little research has focused on the influence on HPA parameters.

We demonstrated that patients taking PI-based regimens revealed a significantly higher cortisol response in acute stress situations than those who took antiretroviral drug regimens without PI. This result is in line with previous studies, which demonstrated that higher cortisol levels were associated with PI treatment (Collazos et al., 2004; Collazos et al., 2003). In general, higher concentrations of base plasma cortisol were detected in patients with antiretroviral treatment compared to untreated patients (Christeff et al., 2000; Collazos et al., 2004; Collazos et al., 2003). Against our expectations, PI users in the treatment group had a higher ACTH reaction than PI users in the control group. Further, within the treatment group, PI user had higher a ACTH response than those without PI. In a recent study, base ACTH levels were found to be elevated in PI associated lipodystrophy syndrome (Yanovski et al., 1999). Thus, our findings suggest that the use of PI regimens in HIV resulted in a dysregulation of the HPA axis. In particular, PI might influence plasma cortisol and ACTH reactions and interfere with the CBSM training effects.

This study bared some limitations. One was the missing clarification of adrenal insufficiency at baseline. The application of an endocrine stimulation test might detect a subclinical manifestation of primary adrenal insufficiency, which is common in HIV infected patients (Eledrisi & Verghese, 2001).

An additional limitation was that we did not measure DHEA-S, which seems to be an important factor of disease progression. According to our results, other studies did not detect cortisol changes after CBSM training (Cruess et al., 1999; D. G. Cruess, M. H. Antoni, N. Schneiderman et al., 2000; McCain et al., 2003), whereas changes in DHEA-S, respectively Cortisol/DHEA-S levels after CBSM have been demonstrated.

Also, we only evaluated two modes of coping, “problem focused” and “emotional-focused coping behaviour". Eventually, the study participants were volunteers and therefore reflect a selective population of HIV infected patients.

In summary we could not demonstrate changes in endocrine and cognitive stress reactions after CBSM training in HIV infected patients under HAART. Antiretroviral regimens especially PI may influence HPA axis activity with the tendency to a higher stress reactivity of patients taking PI treatment.

4. Sympathetic stress response in HIV infected patients under HAART after cognitive-behavioural stress management training

4.1. Introduction

Cognitive behavioural stress management (CBSM) interventions have been shown to ameliorate psychological and physiological parameters in HIV infected persons (Antoni 1991, Antoni 2002, Cruess 2000), which are known to be associated with disease development. Thus, the reduction of stress by improving coping strategies might be an important opportunity to influence the course of HIV infection and decrease the risk of disease progression.

Stressful life events were reported to have a significant influence on disease outcome of HIV infection. The risk of developing HIV related clinical symptoms increases and relevant immune markers decrease during conditions of stress (Evans et al., 1995; Evans et al., 1997; Goodkin et al., 1996; Howland et al., 2000; Ironson et al., 1994; Kimerling et al., 1999; Leserman, 2000; Leserman et al., 1999; Leserman et al., 2002; Leserman et al., 1997; Patterson et al., 1995).

The stress response is characterized, amongst others, by an increased activity of the sympathetic nervous system (SNS), resulting in an increased production of the catecholamines epinephrine (E) and norepinephrine (NE) and an increased activity of the cardiovascular system, intending to prepare the person for the stressor. Yet, prolonged stress exposure and /or unsuccessful coping strategies are supposed to lead to adverse effects on physiological functions, referred to as allostatic load (McEwen & Seeman, 1999).

In HIV disease, previous studies have found some evidence of autonomic dysfunction, which progresses to a significant decline in autonomic function during illness (J. A. Cohen & Laudenslager, 1989; Freeman et al., 1990; M. Kumar et al., 1991; Mittal et al., 2004; Neild et al., 2000). Furthermore, syndromes related to autonomic deregulations, such as cardiovascular diseases, have been demonstrated in the pathogeneses of HIV (Prendergast, 2003), which may reflect allostatic burden in HIV disease.

The reported abnormalities in autonomic function might be caused by infectious stress and/or chronic psychological stress.

HIV might possibly influence autonomic function directly (Chen et al., 2002; Lewis et al., 2005; Prendergast, 2003) or via cytokines (Kan et al., 2000). Additionally, opportunistic infections and HAART might play a destructive role in autonomic functioning (Prendergast, 2003), e.g. the use of PI was shown to increase the risk of cardiovascular disease (Morse & Kovacs, 2006). On the other hand, the sympatho-adrenomedullary system might be a possible mediating factor between psychological stress and disease progression in HIV (Leserman, 2003b). The neurotransmitter NE has been shown to accelerate HIV replication and enhance viral gene expression in vitro (S. W. Cole et al., 1998; S. W. Cole et al., 2001). Furthermore, Cole (1998) could demonstrate that HIV replication by NE is mediated via alteration of the cytokine pattern towards a T_h2 cytokine profile, which in turn is related to

disease progression in HIV (Clerici, Villa et al., 1994; S. W. Cole et al., 1998). Thus, Cole (2001) suggested that neural activity has a direct effect on the course of HIV disease. Additionally, high activity of the ANS in vivo (e.g. systolic blood pressure) was associated with a worsened clinical outcome (viral load and CD4+ cells) after initial HAART (S. W. Cole et al., 2001), supporting the hypothesis that chronically elevated ANS activity in prolonged stress situations might influence HIV progression.

The choice of adaptive coping strategies is supposed to be a relevant factor in HIV development. Some studies have demonstrated that the style of coping is related to clinical parameters of HIV disease progression (Ironson et al., 1994; Leserman, 2000; C. L. Mulder, Antoni, Duivenvoorden et al., 1995; B. F. Sherman et al., 2000; Vassend et al., 1997). Therefore, coping has been discussed as one key factor explaining the variance in HIV disease course.

In consequence, several investigations have examined the effect of CBSM on endocrine and immune functioning (Antoni et al., 2002; Antoni, Cruess, Cruess, Kumar et al., 2000; Cruess et al., 1999; D. G. Cruess, M. H. Antoni, N. Schneiderman et al., 2000), but only one study focused on parameters of the sympathetic nervous system (SNS). Antoni (2000) found that HIV infected men had a greater decline in NE levels accompanied by decreased anxiety after attending the CBSM course. NE changes had partially mediated the effect of immune outcomes at follow-up 6-12 months later, indicating that the modification of the bidirectional relationship between immune system and ANS via changes in the amount of neurotransmitter is beneficial to health in HIV disease (Antoni, Cruess, Cruess, Lutgendorf et al., 2000).

However, this only study focussing on changes in neural activity after CBSM is confined to two parameters representing the autonomic system. Moreover, the effect of CBSM on the symptho-adrenomedullary stress system was not evaluated under conditions of acute stress, so no evidence exists regarding stress reactivity in HIV. Finally, it remains unclear if the intervention effect is transferable to the HAART era.

In healthy subjects it has already been demonstrated that CBSM attenuates stress reactivity during an acute stress test, influenced only by differences in coping strategies (Gaab et al., 2003; Hammerfald et al., 2006).

Therefore, the aim of this investigation was to prove the beneficial effect of a group-based CBSM training on the sympathetic stress response in a standardized stress condition with HIV infected persons undergoing HAART. Thus, we evaluated coping strategies, which might influence perceived stress in an acute stress situation and consequently, the symptho-adrenomedullary stress reactivity. Our aim was to find out if CBSM can change a potential mediator of disease progression in HIV.

4.2 Methods

4.2.1 Subjects

HIV seropositive patients (men and woman) were recruited for study participation from the SHCS-Centre (Swiss HIV Cohort Study) between December 2003 and July 2004. Participants were between the age of 18 and 60, were members of the SHCS and had been taking HAART medication at least 3 months prior to study entry. Exclusion criteria were CD4+ cell count <100, active opportunistic infections, initiating a new psychotherapy in the past 3 months and not being fluent in German.

To ensure that all participants would be appropriate for group CBSM, we also excluded those subjects meeting criteria for mental and behavioural disorders due to psychoactive substance abuse (F10-F19) or major psychiatric diagnosis [i.e., schizophrenia, schizotypal and delusional disorders (F20-F29), manic episode (F30.0), bipolar affective disorder (F31.0), severe depressive episode with or without psychotic symptoms (F32.2, F32.3) personality disorders (i.e. paranoid personality disorder (F60.0) or schizoid personality disorders (F60.1))]. We used a standardized and structured computer-aided version of the Munich composite international diagnostic interview (DIA-X/M-CIDI) (Wittchen & Pfister, 1997) and the SCID II (Wittchen et al., 1997) for psychological screening.

4.2.2 Study design

The study was a randomized controlled trial study (treatment vs. waiting list control condition) with repeated assessment of dependent variables (pre and post training, and 6 months follow-up evaluation). It was conducted in four German speaking Swiss HIV centres (Basel, Bern, St. Gallen, Zürich), representing the German speaking area of Switzerland.

During the recruitment period 1157 patients were eligible for screening. Among those, 102 enrolled in the study and were randomly assigned to either the 12-week CBSM intervention (N=53) or to a waiting-list control condition (N=49; subjects received the CBSM-intervention at the end of the study). Of the remaining eligible patients, 1047 actively refused participating in the study.

Randomization, performed centrally with the use of sealed envelopes containing allocations from a computer-generated table of random numbers, was stratified according to the centre (4) and the CD4+ cell count <200/≥200. A 4:4 ratio of randomization (intervention group: control group) was used. Assignment to study conditions was conducted subsequent to screening.

Among the 102 enrolled subjects, 23 subjects (18 experimental, 5 control) withdrew from the study prior to completion of the intervention, leaving 75 patients to complete the posttreatment assessment. Of those a total of 71 participants patients underwent the Trier social stress test (TSST), which took place one month after completing the CBSM course, subsequent to post assessment.

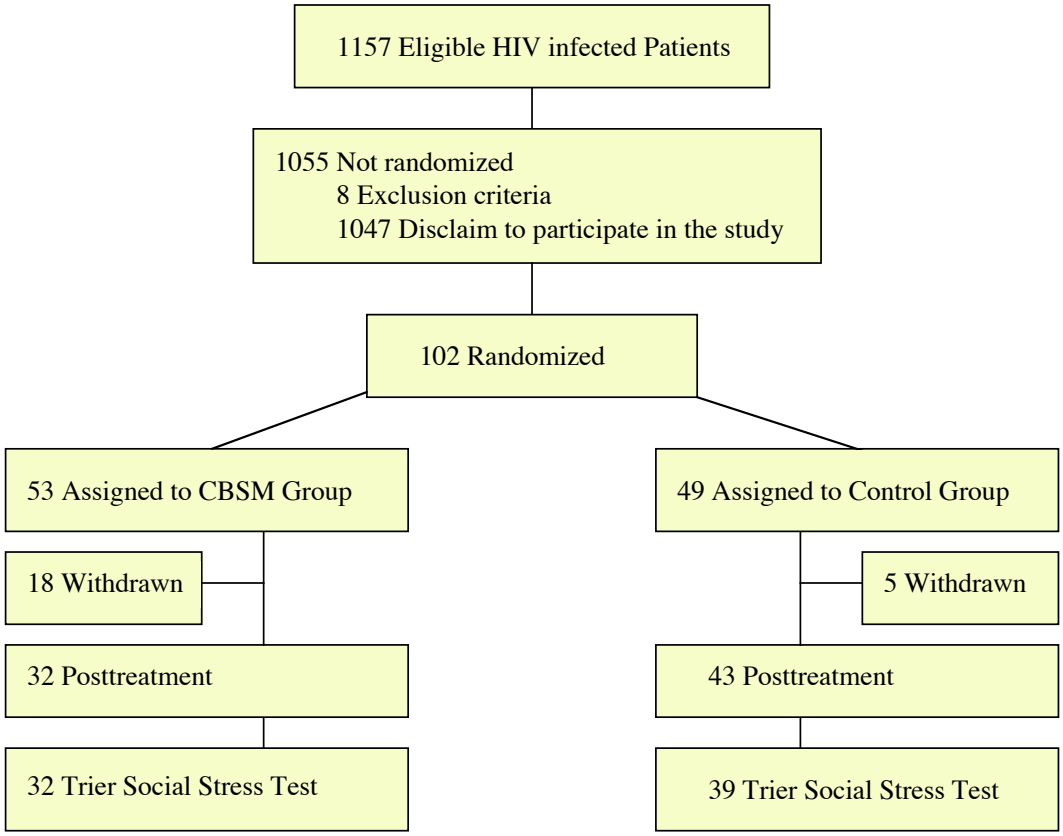

Fig. 2: Flow Diagram of Participant Screening, Randomization, Posttreatment and Trier Social Stress Test

4.2.3 Procedure

4.2.3.1 Cognitive behavioural stress management training:

Cognitive behavioural stress management training (CBSM) is based on the principles of the stress inoculation training developed by Meichenbaum (Meichenbaum & Novaco, 1985) and modified according to F. H. Kanfer`s self management, K. Grawe`s psychological psychotherapy and the HIV group program developed within the scope of the EUROVIHTA-project (Escobar Pinzón, 2000; Grawe, 2002; Kanfer et al., 1996).

CBSM training was a 2-hour, group-based (4-10 subjects per group) intervention, taking place weekly over a 12-week period. The intervention consisted of cognitive-behavioural stress-reducing techniques (cognitive restructuring, problem-solving, self-instruction), assertiveness training, satisfaction of personal needs, strategies for using social support and self-management training. These techniques were practiced along with 10 themes (vertical training modules). Five themes were fixed (1. stress, 2. depression, 3. social support, 4. stigmatization, 5. influence of HIV on personal aims) and five themes were variable (a. medications and their side effects, b. dealing with crisis, sexuality and partnership, c. stress at work or unemployment, d. social competence, e. health behaviour and well being, f. fatigue, g. anxiety, h. death) and were chosen by the group members after the first meeting (introduction ses-

sion). Additionally, each session included group dynamics and progressive muscle relaxation (horizontal training modules).

Each group session had the same schedule, starting with a horizontal training module (group dynamics), followed by a vertical training module (introduction to the current theme) and, after a short break (10 min), followed by another horizontal training module (progressive muscle relaxation), another vertical module (training according the current theme) and eventually ending with a horizontal training module (group dynamics). At the end of each group therapy session participants were given homework, permitting them to practise the learned techniques in real life.

During each session, participants received a summary of the practised theme and the stress-reducing technique, as well as flash cards briefly describing each technique.

Each group was managed by two postdoctoral psychotherapists in training (always one male and one female psychotherapist) according to a training manual.

4.2.3.2 Psychosocial stress test

The Trier social stress test (TSST) consists of an anticipation period (10 mins.) and a test period (a five-minute job application speech and a five-minute unprepared mental arithmetic task performed out loud in front of an audience and a camera).

The TSST has been found to induce profound cortisol, ACTH and cardiovascular responses in 70-80% of subjects (Kirschbaum et al., 1993) and to provoke the most robust physiological stress responses compared with other laboratory stress tasks (Dickerson and Kemeny, 2002)

After arrival at the laboratory, an intravenous catheter was inserted into the subject's forearm to allow for periodic collection of blood samples. After a resting period of 30 minutes a base blood and saliva sample were taken. The subjects were then guided to the TSST room, where they were introduced to the task they would have to perform subsequently (2 mins.). They then returned to a different room, where they were given 10 minutes to prepare and 5 minutes to complete a questionnaire designed to assess cognitive appraisal processes (Primary appraisal secondary appraisal scale, PASA; (Gaab et al., 2005). After spending the preparation in solitude, a second of blood and saliva sample was taken (-11 mins.). Then the subjects started the test period by taking part in a simulated job interview. After five minutes, the task changed to performing serial subtractions of 17 starting at the number 2023. Whenever the subjects made a mistake, they were required to restart at number 2023. Immediately after the 10 minutes test period, the subjects were guided out of the room and a third blood and saliva sample was taken (+1 min). Then the subjects completed a second set of questionnaires (Skala zur Erfassung des Bewältigungsverhaltens SEBV; (Fillip & Ferring, 1989); Ways of coping checklist; (Folkman & Lazarus, 1980) to assess coping behaviour. Subsequently, they were requested to complete a form concerning current substance abuse and medication other than antiretroviral therapy. Further blood and saliva samples were collected at +10 mins., +20 mins., +30 mins., + 45 mins. and + 60 minutes

after the test period. Eventually, the participants were debriefed. The TSST was performed between 13.00 and 19.00 h.

4.2.4 Outcome measures

As dependent measures, we assessed psychological and physiological effects before, during and after the TSST as described subsequently.

4.2.4.1 Control variables and immune parameters

At pre and post training, potentially confounding outcome parameters such as medical characteristics, antiretroviral medications and medical history were assessed at the Swiss HIV centres. Also, demographic variables as well as behavioural and mood data (depression and anxiety; Hospital depression and anxiety scale, HADS-D, Hermann et al., 1995) were collected from patients.

4.2.4.2 Psychological assessment

Anticipatory cognitive appraisal processes in the TSST were assessed with a situation-specific transactional stress questionnaire "primary appraisal secondary appraisal scale" (PASA). This questionnaire consists of one tertiary scale "stress index" which is composed of two secondary scales, "primary appraisal (PA)" and "secondary appraisal (SA)" which are respectively composed of four primary subscales: "challenge (PA)" and "perceived threat (PA)", "Self-Concept of Own Competence (SA)" and "Control Expectancy (SA)". The PASA has a good reliability and validity (Gaab et al., 2005).

To assess the coping behaviour in the TSST, we used the German version of the "Ways of coping checklist" (SEBV: Skala zur Erfassung des Bewältigungsverhaltens). This short version was proven to be adequate in differentiating between emotion-focused (palliative) and problem-focused coping behaviour (Ferring et al. 1989). The SEBV consists of 2 subscales, which are "emotion-focused" (18 items) and "problem-focused" (18 items).

4.2.4.3 Biochemical Analyses

Blood sampling

To determine plasma epinephrine and plasma norepinephrine concentrations, blood samples were collected –30 and -11 minutes before and +1, +10, +20, +30, +45 and +60 minutes after the stress exposure (TSST-test period).

Blood samples were placed on ice and then centrifuged with the plasma pipetted off and stored at –80°C before analyzing the samples.

Catecholamines assay

Plasma concentrations of epinephrine and norepinephrine were determined by high-performance liquid chromatography (HPLC-system from DIONEX, UK) with electrochemical detection after a quantita-

tive isolation of epinephrine and norepinephrine from plasma by liquid-liquid extraction procedure adopted from (Smedes, Kraak, & Poppe, 1982) and slightly modified for the use of lower sample volumes. Typically, the interassay and intraassay variability was in a range of 3% to 5% (coefficient of variation).

4.2.4.4 Haemodynamic measures

Heart rate

Heart rate data was obtained continuously via a portable heart rate monitor (Polar system, S810, Polar, Finland). Heart rate responses were computed from 20 minutes before stress exposure to 45 minutes after cessation of stress.

Blood pressure

Blood pressure and brachial pulse were obtained by non-invasive automatic measurements via a sphygmomanometer (Omron 733, Omron Healthcare Europe B.V., Hoofddorp, The Netherlands).

Both parameters were monitored under resting condition (–55 (sitting), -45 (sitting), -35 (standing), -25 (sitting) and -11 minutes (sitting) before stress exposure) and +1, 10, 20, 30, 45 and 60 minutes (sitting) after the TSST period.

4.2.5 Statistical analyses

Repeated-measures ANOVA (Analyses of variance) and ANCOVA (Analyses of covariance) were performed to analyse autonomic data, with “treatment” as grouping variable and “time” as repeated measure factor. All reported results were corrected with the Greenhouse-Geisser procedure where appropriate (violation of sphericity assumption). One-way ANOVA and ANCOVA were computed for comparison of areas under the curve (AUC).

Areas under the curve were calculated with respect to ground (AUCg = area under all sample), and with respect to increase (AUCi = area under all sample with reference to the first value) for autonomic parameters using the trapezoid formula (Pruessner et al., 2003).

Heart rate data was averaged over 5-minute intervals. Pulse pressure (PP) was calculated by the difference between systolic (SB) and diastolic blood pressure (DB) (PP = SB-DB).

Data was tested for normal distribution and homogeneity of variance using a Kolmogorov-Smirnov and Levene`s test before statistical procedures were applied. In case of non-normal or skewed distribution ln-transformation for endocrine and autonomic parameters, log-transformation for viral parameters (RNA) and square root transformation for immune and psychometric parameters were performed.

The two groups were compared with respect to demographic, behavioural, psychological and medical characteristics using the chi-square-test for categorical data, Mann-Whitney-U-test for ranked data or not normally distributed variables and one-way analysis for continuous data. Descriptive statistics

included percentage for categorical data, median and range for ranked data and mean values (+/-SD) for continuous data. Means and standard deviations of untransformed values are presented.

Some data was missing because of equipment problems, difficulties in taking blood samples and failed biochemical analysis so that the analyses are based on 59 subjects for the parameters norepinephrine, epinephrine, systolic and diastolic blood pressure, 51 subjects for the parameter pulse, 66 subjects for parameters in heart rate. Statistical significance of all analyses was set at .05. All statistical analyses were performed using SPSS version 11.04 for Macintosh.

4.3 Results

4.3.1 Sample characteristics

There were no group differences in gender, age, body mass index, education, income, sexual orientation or nationality between treatment and control group (see table 1). Also no statistical differences in aerobic exercise and current substance abuse were detected (see Table 2). As well, subjects in the treatment group did not differ in medical characteristics at baseline and post assessment, current medication and medical history (see Table 3). No differences in depression and anxiety score were found at post training evaluation. However the samples varied in the use of antiretroviral regimen at post assessment ($\chi^2 = 3.90$; $P = 0.05$) (see table 3). At the time of the psychosocial stress test 40, 6% of the treatment group were taking protease inhibitors, whereas the waiting list control group showed a greater proportion (65,1%).

4.3.2 Effect of CBSM training on autonomic stress reaction

4.3.2.1 Catecholamine response to stress

The autonomic response after stress exposure did not differ notably between patients assigned to CBSM training compared to those in the control group.

A significant increase in catecholamine after the TSST was observed (time effect: epinephrine: $F_{(1.91/104.80)} = 44.934$; $P < .000$; norepinephrine: $F_{(4.44/253.00)} = 77.171$; $P < .000$) in all patients (see fig. 9 and 10).

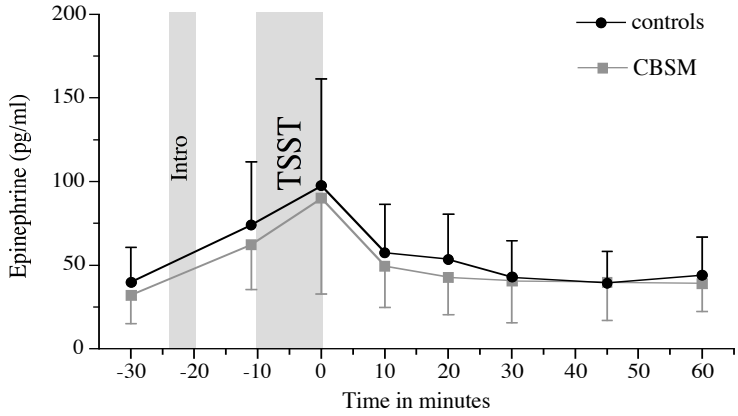

Fig. 9: Epinephrine responses in the TSST

No significant differences in norepinephrine reactivity (group by time interaction effect: $F_{(1.91/104.80)}$ = 0.511; P = .592) and epinephrine reactivity over time (group by time interaction effect: $F_{(4.44/253.00)}$ = 1.081; P = .369) between the treatment and the control groups could be detected (see table 9).

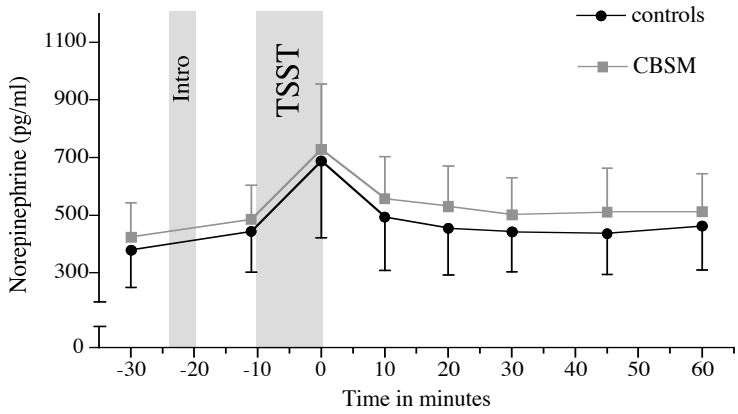

Fig. 10: Norepinephrine responses in the TSST

Table 9: Results of autonomic response to stress in treatment and control group

	Time effect	Group x time interaction	Group effect
Epinephrine	F (1.91/104.80) = 44.934; P < .000*	F (1.91/104.80) = 0.511; P = .592	F (1/55) = 1.039; P = .313
Norepinephrine	F (4.44/253.00) = 77.171; P< .000*	F (4.44/253.00) = 1.081; P = .369	F (1/57) = 3.259; P = .076

In line with these results, neither the areas under the curve of norepinephrine (group effect AUCg: $F_{(1/57)}$ = 2.336; P = .132; group effect AUCi: $F_{(1/57)}$ = 0.405; P = .527) nor the areas under the curve of epinephrine (group effect AUCg: $F_{(1/55)}$ = 0.989; P = .324; group effect AUCi: $F_{(1/55)}$ = 0.081; P = .778) differed between the groups (see table 10).

Table 10: Group comparisons of the areas under the curve parameters

	Parameter	CBSM group [a]	Control group [a]	Statistic
Epinephrine (pg/ml)	AUGg	4492 (2012)	5072 (2283)	F (1/55) = 0.989; P = .324
	AUCi	1597 (1684)	1474 (1545)	F (1/55) = 0.081; P = .778
Norepinephrine (pg/ml)	AUGg	47523 (11076)	42448 (13606)	F (1/57) = 2.336; P = .132
	AUCi	9316 (7669)	8287 (4709)	F (1/57) = 0.405; P = .527

[a] Mean (standard deviation)

In consequence of the differences in antiretroviral PI regimens, PI was analysed as potentially moderator of outcome (Kreamer H 2002, 2006). Moderation was tested by hierarchical regression equation as described by Cohen (J. Cohen, Cohen, P., West, S. G., Aiken, L.S., 2003). Significant interaction was analysed using simple effects analysis (see (Baron & Kenny, 1986).

We could not detect a significant group by PI interaction for AUCg norepinephrine. However, we found an overall effect of PI on AUCg norepinephrine ($R^2_{adjust.}$= .16, $F_{(3/55)}$ = 4.705, p = .005; PI-treatment effect: ß = -.417, t = -2.217; p = .031). Therefore, PI was classified as a non-specific predictor of norepinephrine reaction (Kraemer et al., 2002). Patients with PI-based regimens showed a lower norepinephrine response in acute stress situations than those who took antiretroviral drug regimens without PI (see fig. 11).

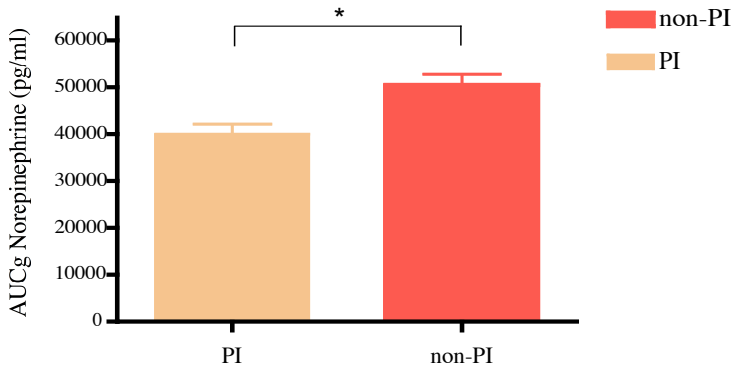

Fig. 11: Norepinephrine in the TSST; comparison between PI user and non-PI user

A significant disordinal group by PI-treatment interaction was identified for AUCg epinephrine (see table 11). Consequently, PI was a moderator of CBSM treatment. Simple effects analyses revealed that treatment influenced the epinephrine response for non-PI users ($F_{(1/54)}$ = 2.29; P = .025), but not for the PI user condition ($F_{(1/54)}$ = 0.63; P = .431), such that the mean for the CBSM group was lower than for the control group within non-PI users (see fig. 12). Further analysis demonstrated a significant difference between PI users and non-PI users within the treatment group ($F_{(1/54)}$ = 5.30; P = .025), but not within the control group ($F_{(1/54)}$ = 2.29; P = .025).

Table 11: Summary of Hierarchical Regression Analysis for Variables Predicting AUCg Epinephrine (N = 57)

Variable		B	SE B	ß
Step 1				
	Constant	4492.18		
	Group	580.01	583.28	.13
Step 2				
	Constant	4340.24		
	Group	499.89	601.05	.12
	PI use	364.67	595.80	.08
Step 3				
	Constant	3706.61		
	Group	1872.77	827.34	.43*
	PI use	1885.39	870.75	.44*
	Group x PI use	-2682.39	1156.45	-.60*

Note. R^2 = .02 for Step 1; ΔR^2 = .01 for Step 2 (*p*s = .54) ; ΔR^2 = .10 for Step 3 (*p*s < .05). *p < .05

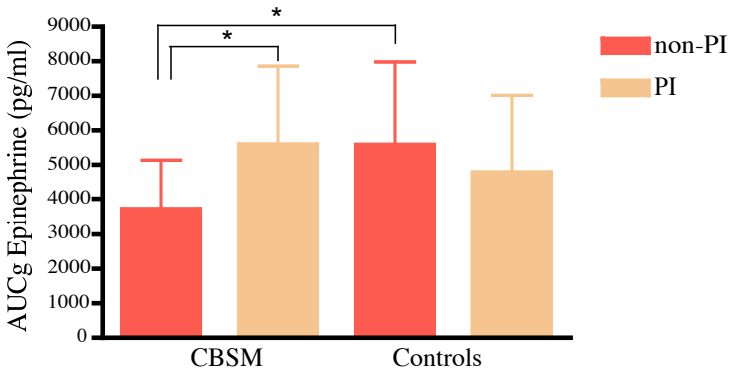

Fig. 12: Epinephrine in the TSST; group by PI-treatment interaction

4.3.2.2 Haemodynamic responses to stress

The TSST elicited a significant increase in HR ($F_{(3.88/213.22)}$ =70.261; P< .000), in diastolic BP ($F_{(7.56/431.10)}$ = 12.931; P < .000), in systolic BP ($F_{(6.46/368.29)}$ = 12.197; P < .000), in pulse pressure ($F_{(10/570)}$ = 4.608; P = .000) and pulse ($F_{(7.11/348.15)}$ = 12.274; P < .000) (see table 12, see fig. 13 A-E).

Table 12: Results of autonomic response to stress in treatment and control group

	Time effect	Group x time interaction	Group effect
Heart rate	F (4.39/289.46) = 98.663; P < .000*	F (4.39/289.46) = 0.480; P = .767	F (1/66) = 0.833; P = .365
Diastolic blood pressure	F (7.56/431.10) = 12.931; P < .000*	F (7.56/431.10) = 1.427; P = .187	F (1/57) = 0.217; P = .643
Systolic blood pressure	F (6.46/368.29) = 12.197; P < .000*	F (6.46/368.29) = 1.326; P = .241	F (1/57) = 0.611; P = .437
Pulse	F (7.11/348.15) = 12.274; P < .000*	F (7.11/348.15) = 1.904; P = .067	F (1/49) = 0.516; P = .476
Pulse pressure	F (10/570) = 4.608; P = .000*	F (10/570) = 0.607; P = .779	F (1/57) = 3.252; P = .077

However both groups did not differed in their haemodynamic stress response. No significant differences were found in HR, diastolic and systolic blood pressure, pulse and pulse pressure between groups in the TSST (see table 12). However, the groups showed a trend to differ in their overall pulse pressure response (group effect: $F_{(1/57)}$ = 3.252; P = .077) and their pulse stress response over time (group by time interaction: $F_{(7.11/348.15)}$ = 1.904; P = .067).

These results were consolidated by the lack of significant group effects of AUCg in all haemodynamic parameters (see table 13) and a trend toward a significant difference in AUCg pulse pressure ($F_{(1/57)}$ = 3.486; P = .067).

Table 13: Group comparisons of the area under the curve parameters with respect to ground

	CBSM group [a]	Control group [a]	Statistic
Pulse (beats/min)	8556 (1124)	8791(1124)	F (1/49) = 0.556; P = .460
Heart rate (beats/min)	5998 (818)	6185 (887)	F (1/64) = 0.783; P = .379
Diastolic blood pressure (mm/Hg)	9836 (822)	9684 (1153)	F (1/57) = 0.321; P = .573
Systolic blood pressure (mm/Hg)	14494 (1382)	14798 (1714)	F (1/57) = 0.538; P = .466
Pulse pressure (mm/Hg)	4658 (911)	5113 (944)	F (1/57) = 3.486; P = .067

[a] Mean (standard deviation)

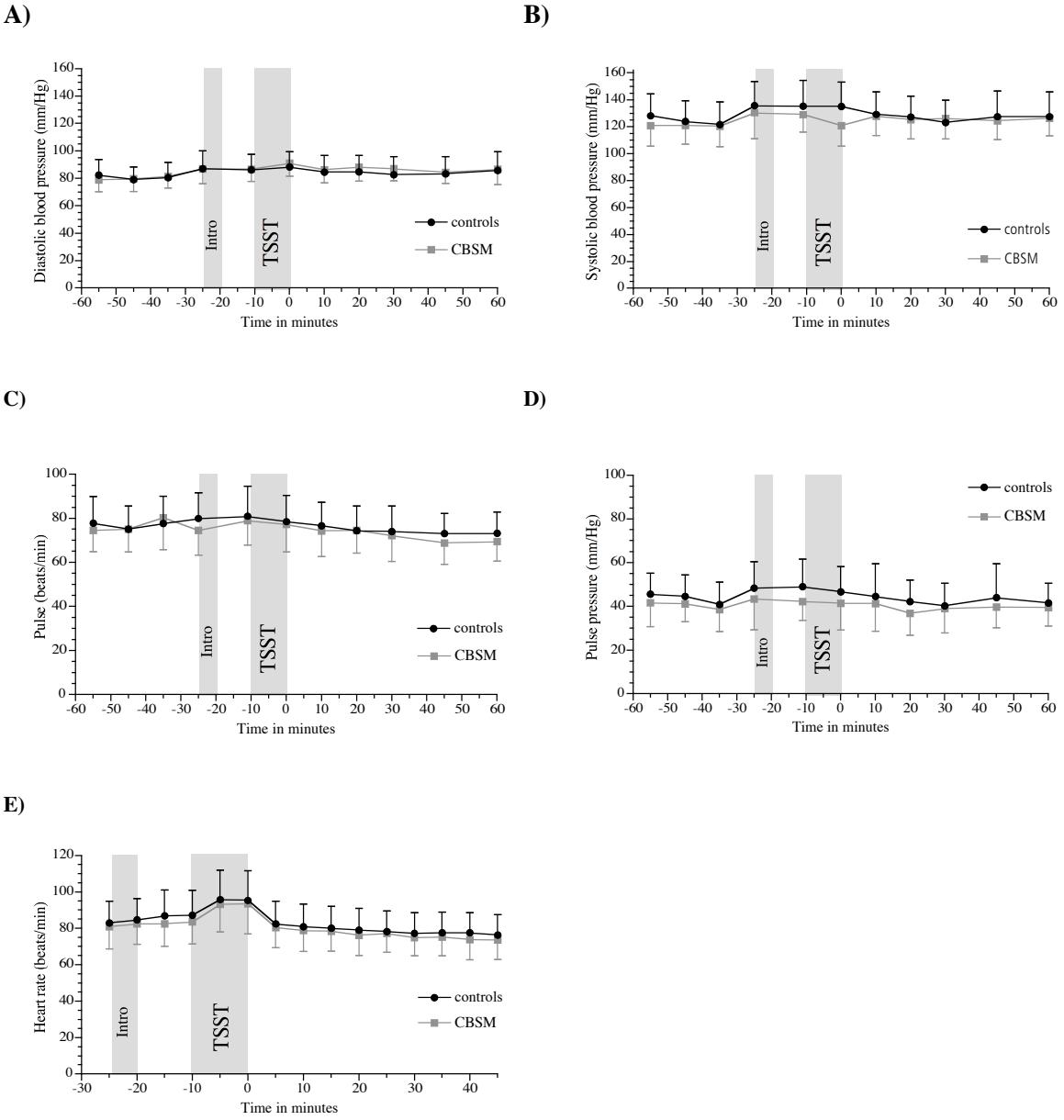

Fig. 13: A) Diastolic blood pressure in the TSST; B) Systolic blood pressure in the TSST; C) Pulse in the TSST; D) Pulse pressure in the TSST; E) Heart rate in the TSST

In a second step, possible confounding variables or variables, probably reducing the error variance have been identified via hierarchical linear regression analysis. The use of heart medication, BMI and age, which are known to influence haemodynamic parameters, were entered into a regression analysis. If one of those variables revealed as significant predictor, it was entered into the analysis as covariate.

We determined the variable age as a significant predictor for pulse pressure, the variable BMI as significant predictor for diastolic blood pressure and the variables age and BMI as significant predictors for systolic blood pressure. No significant predictors were identified for the dependent variables heart rate and blood pressure.

Repeated-measures ANCOVA revealed the lack of significant differences between the CBSM group and the control group in systolic blood pressure (group by time interaction effect: $F_{(6.61/363.71)}$= 1.407; P = .205; group effect: $F_{(1/55)}$= 2.338; P = .132) and in diastolic blood pressure (group by time interaction effect: $F_{(7.56/432.41)}$= 1.434; P = .184; group effect: $F_{(1/56)}$= 0.002; P = .966).

In contrast, after controlling for age, pulse pressure differed between the treatment and the control group (group effect: $F_{(1/56)}$= 4.521; P = .038; η = .075) (see fig. 14). Patients in the treatment group showed a significant lower pulse pressure during TSST compared to the control group. Furthermore, one-way ANCOVA revealed a significant lower AUCg of pulse pressure in patients receiving CBSM compared to controls (group effect: $F_{(1/56)}$= 5.079; P = .028; η = .083).

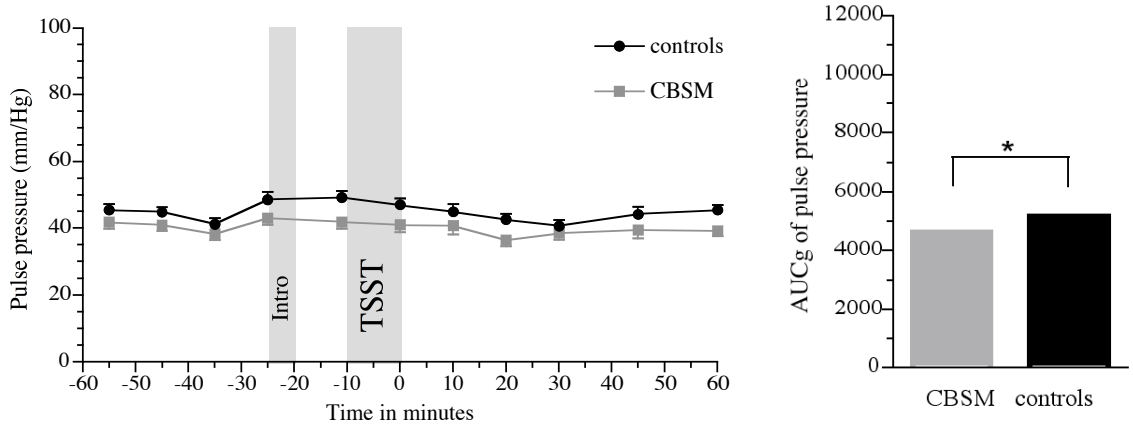

Fig. 14: Pulse pressure in the TSST (controlling for age)

The use of PI did not moderate the effect of treatment on haemodynamic parameters. Hierarchical regression analysis demonstrated no significant group by PI interaction on diastolic blood pressure, systolic blood pressure, pulse, pulse pressure and heart rate (data not shown).

4.3.3 Effect of CBSM training on cognitive appraisal and coping

As already mentioned, groups did not differ in cognitive appraisal and coping style after the CBSM training. No group differences were found with respect to secondary PASA scales and PASA stress index (see Table 7). The primary scale "challenge" was significantly lower in the treatment group compared to the control group (group effect: F (1/69) = 3.837; P = .054, r = .23). The other three primary scales (threat, challenge, self-concept) were equal in both groups. We also detected no differences between the two groups in the SEBV scales "emotion-focused coping behaviour" and "problem-focused coping behaviour" (see Table 8).

4.4 Discussion

In this randomized controlled trial we examined the effect of group-based CBSM training on sympathetic and cardiovascular reactivity to acute stress in HIV infected patients under HAART. Therefore, patients assigned to either the CBSM or the control group underwent a social stress test, taking place one month after the completion the CBSM training.

In summary, results indicated no differences in norepinephrine and epinephrine reactions in the TSST between treatment and control groups for all HIV-patients. However, a subgroup of patients using antiretroviral drug regimes without PI-based regimens benefited from the CBSM training by a reduced epinephrine stress response.

No differences were found in haemodynamic parameters (heart rate, systolic and diastolic blood pressure, pulse and pulse pressure) between both groups before controlling for confounding variables. However, when controlling for confounds, patients in the CBSM group revealed lower pulse pressure during the TSST than controls.

Further, patients assigned to the CBSM training appraised the stress situation as less challenging compared to the control group. However, there were no differences in secondary PASA scales (primary and secondary appraisal), stress index, emotion-focused coping behaviour and problem-focused behaviour.

HAART regimens of our HIV population might be responsible for the delineated sympathetic stress responses.

In our study, the administration of PI-based regimens was not equivalent in both groups. Therefore, we examined the potential influence of PI on endocrine and haemodynamic parameters.

As specified by moderation analysis, PI was detected as a non-specific predictor for the norepinephrine response under acute stress. Patients who were taking PI-based regimens demonstrated lower norepinephrine response than those without.

Furthermore, PI was identified as a moderator for epinephrine in the acute stress response. Only the non-PI users profited from the CBMS training, i.e. patients taking no PI who were assigned to CBMS training showed a significant lower epinephrine reaction in comparison to the waiting list control group taking no PI. Thus, the effect of the CBSM training on the epinephrine response under acute stress decreased in patients taking antiretroviral drug regimes with PI.

The particular combination of antiretroviral drug regimes has various influences on clinical side effects and physiological outcomes (Dube et al., 2005; P. N. Kumar et al., 2006; Willard, 2006). Yet, research is still in progress and evidences concerning the effect of several antiretroviral drug regimens were marginal. Thus, little is known about the influence of PI on catecholamines. Fliers (2003) demonstrated a regional increase in norepinephrine concentrations in skeletal muscle and subcutaneous fat tissue in patients with HARS (HIV associated adipose redistribution syndrome) due to the toxic effect of ART (Fliers et al., 2003). Catecholamine-stimulated lipolyse in HIV infected patients with lipodys-

trophy might be a result of the use of PI (Adler-Wailes et al., 2005). In general, an increase of risk factors for cardiovascular diseases has been associated with PI use (Friis-Moller et al., 2003; Glass et al., 2006; Hadigan et al., 2003; Sattler et al., 2001). Thus, our results confirm the influence of PI on the sympathetic system.

Treatment and control group differed in their overall pulse pressure when controlling for confounding variables, i.e. the CBSM group revealed a reduced pulse pressure under acute stress. Pulse pressure increases due to interaction of cardiac ejection and properties of the arterial circulation (Dart & Kingwell, 2001). Elevated pulse pressure is seen as a risk factor for cardiovascular disease (Franklin, Khan, Wong, Larson, & Levy, 1999; Haider, Larson, Franklin, & Levy, 2003) and consequently of increased artery stiffness (Dart & Kingwell, 2001). The normal value for pulse pressure in healthy people is < 50 mm/HG (Asmar, Vol, Brisac, Tichet, & Topouchian, 2001) and is not exceeded by both groups. Nevertheless, a decreased pulse pressure in the CBSM group under acute stress might be a preventive factor, reducing the risk of cardiovascular disease. Especially since subclinical cardiovascular autonomic dysfunction were common in HIV infected patients due to either HIV itself or antiretroviral treatment (Freeman et al., 1990; Friis-Moller et al., 2003; Glass et al., 2006; M. Kumar et al., 1991; Prendergast, 2003). In this context, studies demonstrated global autonomic dysfunction; such as a decrease in heart rate variability in HIV infected patients without clinical manifestation of a cardiovascular disease (Mittal et al., 2004; Neild et al., 2000).
Although HAART, in particular PI, is associated with elevated blood pressure (Crane, Van Rompaey, & Kitahata, 2006; Palacios et al., 2006; Sattler et al., 2001; Seaberg et al., 2005) and increased aortic stiffness (Schillaci et al., 2005), we could not find an impact of PI on any hemodynamic measures.

The missing treatment effect of the remaining haemodynamic parameters, i.e. heart rate, diastolic and systolic blood pressure and pulse, as well as the lack of changes in cognitive stress responses may be a consequence of the CBSM training itself.
The insufficient practise of stress reduction techniques during the CBSM course for HIV infected patients (only 2 hours), when compared to previous studies (2 days) with healthy subjects (Gaab et al., 2003; Hammerfald et al., 2006) may be a reason for the lacking effect of the training.
Further, the practise of cognitive techniques in the present CBSM training was not focused on the acute stress situation. The training was directed to ameliorate cognitive strategies along themes like depression, social support, and stigmatization that were known to influence the course of HIV disease. Thus, we assumed that the lower challenge perception under acute stress reflected the attenuated common challenge perception, including acute stress situations. Yet, consequently we should put the TSST into question to be an appropriate instrument to evaluate our CBSM training. Particularly, in view of the fact that endocrine stress reactions in laboratory studies are not completely comparable to naturalistic daily stressors (Smyth 1998).

A first methodological limitation of this study was the restriction that the sample only consisted of volunteer HIV infected patients, which might have produced a selection bias.
Second, in contrast to previous studies, the examined population was characterized by several variables that might have interfered with the dependent variables. In order to ensure generalizability, we nevertheless enclosed all patients. Although we tried to minimize potential confounding, there might be the possibility of unknown or unmeasured factors, which possibly influenced results.
Third, we assessed the cognitive stress response only with two questionnaires. One of these questionnaires, the PASA, is validated only with regard to the plasma cortisol response (Gaab et al., 2005). These results might not be transferable onto the SAM system. Findings of a dissociated stress habituation pattern of the HPA axis compared to SAM parameters (Schommer, Hellhammer, & Kirschbaum, 2003) encouraged the hypothesis that both axes are a result of different coping and appraisal strategies. Hence, we neglected to apply more adequate measurement that indicates cognitive stress response for SAM.
Forth, we did not measure a possible important control variable: the frequency of exercise (i.e. progressive muscle relaxation, problem solving). It is more likely that patients, who practise the learned techniques at home, adopt them in real life situations and alter their cognitive behaviour.

In conclusion, a subgroup of non-PI-based antiretroviral regimens profited from CBSM training by a reduced epinephrine stress response. Additionally, a reduced pulse pressure demonstrated the beneficial effect of the CBSM training.
In future, the modification in pulse pressure via CBSM might be an important way to reduce the risk of cardiovascular disease, which is typically increased with the use of HAART in HIV infected patients.

5 General discussion

The aim of this study was to evaluate the effect of group-based CBSM training on the acute HPA and SAMS stress responses in HIV infected patients under HAART. Our intention was to answer the question whether CBSM training could influence possible direct endocrine and autonomic mediators of health outcome in HIV disease.

A number of studies demonstrated that stressful life experiences and emotional distress have a profound impact of disease progression in HIV (Evans et al., 1995; Evans et al., 1997; Goodkin et al., 1996; Howland et al., 2000; Ironson et al., 1994; Kimerling et al., 1999; Leserman et al., 1999; Leserman et al., 2000; Leserman et al., 2002; Leserman et al., 1997). Dysregulation of the HPA and SAMS were discussed as potential mechanisms underlying the adverse effect of stress on disease progression and mortality in HIV (Leserman, 2003b; Petitto et al., 2000; Prendergast, 2003).

Several studies have examined the effect of CBSM on endocrine, autonomic and immune functioning. These were mostly performed at the research centre of the University of Miami (Antoni, Cruess, Cruess, Lutgendorf et al., 2000; Antoni, Cruess, Cruess, Kumar et al., 2000; Cruess et al., 1999; D. G. Cruess, M. H. Antoni, B. A. McGregor et al., 2000; D. G. Cruess, M. H. Antoni, N. Schneiderman et al., 2000), concluding mainly that CBSM might benefit health outcome in HIV infected persons. However, other research teams could not detect such definite results, especially concerning alterations of immune parameters after CBSM training (Coates et al., 1989; McCain et al., 2003; C. L. Mulder, Antoni, Emmelkamp et al., 1995). Further, previous clinical studies in HIV have never evaluated the effect of CBSM training in conditions of stress. All parameters were always recorded during a resting phase. In healthy subjects it has already been demonstrated that CBSM attenuates stress reactivity during an acute stress test, whereby differences in stress appraisal exerted an important influence (Gaab et al., 2003; Hammerfald et al., 2006). Therefore, we decided to evaluate possible CBSM-induced changes in the HPA axis and SAMS reactivity under an acute laboratory stressor (TSST). With this design we aimed at finding profound evidence for alterations of direct mediators affecting health in HIV patients.

This chapter focuses on the results of the two studies presented and interprets the findings while taking into account previous and current research. Further, methodological issues and limitations of the studies will be discussed, concluding with the implication for clinical relevance of the reported findings.

5.1 Summary of the results

Both studies examined the impact of CBSM training on direct mechanisms mediating HIV disease progression. While the first study focused on alteration of the HPA axis, the second study evaluated changes of the autonomic nervous system in HIV infected patients under HAART.

5.1.1 Sympathetic stress response in HIV infected patients under HAART after CBSM training

The purpose of the study was to investigate stress-reducing effects of CBSM on the HPA axis in HIV infected patients under HAART.

Therefore, HIV infected patients were recruited by the four German speaking Swiss HIV centres and were randomized either to the CBSM treatment or control group at study entry. A total of 71 HIV infected patients underwent the Trier social stress test (TSST), which took place one month after completing the CBSM course.

The TSST, a standardized social stress test, has been found to induce a profound cortisol and ACTH increase (Kirschbaum et al., 1993) and to provoke the most robust physiological stress responses compared with other laboratory stress tasks (Dickerson & Kemeny, 2004).

In summary, the findings revealed that CBSM had no effect on endocrine stress parameters. Plasma and salivary cortisol reaction as well as ACTH responses did not differ between treatment and control groups. Both groups did not vary in coping style and cognitive appraisal with exception of the primary scale “challenge” where the treatment group scored less.

However, the use of antiretroviral PI-based regimens differed between both groups. Analysis of moderating effects of PI-based regimens confirmed PI as a moderator of ACTH reactivity and as nonspecific predictor of the plasma cortisol response under acute stress.

We conclude that CBSM training cannot alter either endocrine stress reactions of the HPA or coping behaviour during acute stress. Furthermore, PI-based regimens may intensify the HPA stress reactivity in HIV-infected patients.

5.1.2 Sympathetic stress response in HIV infected patients under HAART after CBSM training

The aim of the second paper was to examine the autonomic stress response after CBSM training in HIV infected persons under HAART. Using the same sample of HIV infected patients on HAART performing the TSST, we now focused on the evaluation of endocrine and hemodynamic parameters of the sympathetic stress system.

Results of these evaluations indicated no differences in norepinephrine and epinephrine stress reactions between treatment and the control groups. However, the catecholamine response might depend on the kind of antiretroviral treatment used. Moderator analysis revealed PI as a non-specific predictor of the norepinephrine reaction for all patients. Also, we could detect PI as a moderator of the epinephrine response. In a subgroup of patients not taking PI, we showed that patients assigned to the CBSM group had a reduced epinephrine reaction compared to the wait-list control group.

Additionally, patients in the CBSM group revealed lower pulse pressure during TSST compared to controls.

In sum, we conclude that CBSM training might be a favourable intervention in reducing pulse pressure, an indicator for cardiovascular risk, which increases continuously in HAART treated patients. Further, a subgroup of non-PI users might benefit from CBSM intervention by a reduced epinephrine response in acute stress situations.

5.2 Methodological considerations and limitations of the study

The biggest challenge in investigating the role of psychological interventions in HIV infected population is to control for the numerous confounding variables while simultaneously minimizing the highly selective recruitment.

Most studies in the pre-HAART area (Antoni, Cruess, Cruess, Lutgendorf et al., 2000; D. G. Cruess, M. H. Antoni, N. Schneiderman et al., 2000) had a wide range of exclusion criteria, such as prior diagnosis of AIDS, regular use of medication other than antiretroviral medication, low doses of psychotropics (substances with known effects on the endocrine or immune systems; e.g glucocorticosteroids or beta blockers), changes in medication status, chronic illness associated with persistent generalized lymphadenopathy, alteration of the immune system (e.g. cancer, type1 diabetes mellitus, asthma, hepatitis, autoimmune diseases) or a history of heavy cigarette smoking (e.g. more than 50 pack years). These exclusion criteria were well selected as each of it has a direct influence on the physiological parameters of interest. Considering our sample characteristics (see tables 1-3), it seemed unlikely that HIV infected persons existed that met all these criteria. A patient passing all exclusion criteria is unrealistic, especially in the HAART-era, which is accompanied by a number of antiretroviral side effects. These side effects increase the need of both medications other than HAART and changes in antiretroviral therapy to handle the side effects. In the case of our study we would have lost the complete sample using such exclusion criteria.

Thus, previous studies had limited test participants due to their exclusion criteria. The samples mostly consisted of relatively healthy, highly educated gay men, which in consequence lead to limited generalizability to other HIV infected populations.

In order to assure generalizability (or external validity) we applied a randomized controlled trial with moderate exclusion criteria for study entry and included all patients in the analyses who took part in the TSST.

Additionally, to prevent potentially confounding variables from producing a bias estimate of treatment effect, stratification of randomization has been carried out with the stratifying factor “stage of disease” (CD4+ cell count <200/ >200) that may affect the outcome.

Further, possible confounding variables or variables potentially reducing the error variance were identified via hierarchical regression analysis. Variables becoming significant predictors were entered as covariates into the analysis.

Despite stratification, antiretroviral treatment (PI) was not balanced within the two groups. Therefore moderator analysis was performed as described by Cohen (2003). Significant group by PI interaction was analysed using simple effects analyses (Baron and Kenny 1986).

Although we tried to ensure internal validity, we cannot exclude that there were still unknown, unmeasured or uncontrollable factors (e. g. the time of infection is usually indeterminable), which might influence dependent variables. A possible important control variable we did not measure is the frequency of exercise (i.e. progressive muscle relaxation, problem solving). It is more likely that patients, who practise the learned techniques at home, adopt them in real life situations and alter their cognitive behaviour.

A further methodological limitation of the study is the missing clarification of adrenal insufficiency and autonomic dysfunction at baseline. The application of endocrine stimulation tests might detect subclinical and clinical manifestations of primary adrenal insufficiency, which is common in HIV infected persons and increases with the disease's progression (Eledrisi & Verghese, 2001). Hemodynamic and autonomic function tests should be used to identify autonomic dysfunction, which also increases with the progress of HIV disease.

Furthermore, we missed to use questionnaires assessing cognitive stress response of the SAMS. The sympathetic axis reflects the activation in consequence of motor and cognitive efforts often described as a "positive stress reaction" (de la Torre, 1994; Linden, Earle, Gerin, & Christenfeld, 1997). In contrast, the HPA axis reflects affective distress and might be a result of chronic, unresolved strain (de la Torre, 1994; Henry, 1975; Linden et al., 1997). Findings of a dissociated stress habituation pattern of the HPA axis compared to SAM parameters (Schommer et al., 2003) encouraged the hypothesis that both axes are a result of different coping and appraisal strategies. The PASA is validated by plasma cortisol response (Gaab et al., 2005). However, these results might not be transferable onto the SAM system.

Lastly, we did not measure DHEAS, an important endocrine HIV disease marker of the adrenal gland (Christeff et al., 1997; S. Grinspoon et al., 2001). Findings indicated that DHEAS might be more susceptible to modifications in HIV compared to cortisol (Cruess et al., 1999).

Additionally, there were potential issues that can affect external validity, e.g. there still might be a selection bias, as the sample consisted only of volunteer HIV infected patients (i.e. low ratio of randomised patients (102) to eligible nonrandomized patients (1157)). Moreover all patients were study participants of the SWISS HIV Cohort Study (i.e. selection of participating centres), which might not be representative for the whole HIV infected population.

5.3 Discussion of the results

One explanation for the missing treatment effects on endocrine stress parameters and cognitive stress assessments for all randomized patients might be found in the CBSM training itself.

In contrast to studies with healthy subjects (Gaab et al., 2003; Hammerfald et al., 2006), in which the CBSM training mainly focused on stress-reduction techniques over a 2-day session, the CBSM training for HIV infected persons consisted only of one session (2 hours) aiming at stress reduction techniques. Further, cognitive techniques focussed other themes like depression, social support or stigmatization to improve the person's coping capacity in different areas. The intention was to convey a broad range of coping strategies for several life situations that might be encountered.

Thus, we interpreted the difference in the subscale "challenge" between the two groups as a result of attenuated common challenge perception, which may reflect a generally relaxed attitude when exposed to different life situations, including acute stress situations. It is thus possible that the probability of middle-aged men to appraise their problems as challenges (Aldwin et al., 1996) is reduced as a result of the CBSM training.

Taking into account that the CBSM training was aimed to reduce stress in common or difficult life situations, it may be questioned that the TSST constitutes an adequate method to evaluate the effectiveness of our CBSM training. The TSST generally provokes a robust stress response (Kirschbaum 1993, Dickerson and Kemeny, 2002), but it does not reflect a naturalistic daily stressor (Smith, 1998).

Beside the reduced focus on stress situations during the CBSM training, characteristics of randomized patients might be a potential reason for the missing treatment effect on endocrine and cognitive stress responses during the TSST.

First, differences in demographic characteristics between the healthy CBSM populations of previous studies (Gaab et al., 2003; Hammerfald et al., 2006) and the present HIV infected population might be responsible for the absence of changes in endocrine parameters as well as in coping style and PASA stress-index. Mean age was much higher in the HIV population (44 years), compared to younger, healthy adults (about 23 years).

Age differences in coping strategies have been found (Blanchard-Fields & Irion, 1988; Diehl et al., 1996; Folkman et al., 1987) and might base on modifications in coping strategies during development. For example in non-controllable situations, coping style might change with age, with a tendency for emotional-focused behaviour in young adults shifting towards a preference for problem-focused behaviour in mature adults (Blanchard-Fields & Irion, 1988). This lead us to the assumption that changing the way of coping and appraisal through CBSM is more likely in younger adults because they are still in a development process of coping behaviour. In contrast, coping behaviour and appraisal might be less flexible in mature adults, as they have already more or less fully developed coping-strategies.

Additionally, age has been found to determine endocrine parameters of the HPA axis. Stress reactivity (Gotthardt et al., 1995; Kudielka, Buske-Kirschbaum, Hellhammer, & Kirschbaum, 2004) as well as basal parameters (Deuschle et al., 1997) differed depending on age. During climacteric, modification of adrenal gland tissues, i.e. enlargement of the zona fasciculata, might result in alterations of cortisol production and HPA-feedback mechanisms. In consequence, CBSM training-induced changes in endocrine stress reactions might have been less likely in older participants.

Another important variable that might have contributed to the missing treatment effect for HIV infected patients is the variety in current medical characteristic, particularly PI-based regimens, between the CBSM-training and the control patients.

Unfortunately, both groups differed in the percentage of HAART regime containing PI, with more PI users in the control group. For both stress systems we detected an influence of PI-based regimens on the stress reaction. In patients taking PI, the plasma cortisol reaction was higher and the norepinephrine response was lower compared to patients without PI treatment.

Presently, studies examining the influence of HAART on stress parameters are rare and the underlying mechanisms are still being explored. In line with our results, Collazos et al. (2003, 2004) demonstrated that higher cortisol levels were associated with PI treatment. (Fliers et al., 2003) supposed a regional increase in norepinephrine concentrations in skeletal muscle and subcutaneous fat tissue in patients with HARS due to the toxic effect of ART. Catecholamine stimulated lipolysis in HIV infected patients with lipodystrophy might be a result of the use of protease inhibitors (Adler-Wailes et al., 2005). The use of PI is associated with a number of side effects, such as LD syndrome, hyperlipidaemia and insulin resistance (A. Carr, 2000; A. Carr, Samaras, Burton et al., 1998) and an increase of cardiovascular risk factors. Thus, the use of PI is related to an increased probability of cardiovascular disease (Sattler et al., 2001). The summarized studies also indicated an impact of antiretroviral PI-based regimens on endocrine parameters of the SAMS and HPA axes.

Accordingly, in our study, the subgroup of patients without PI-based regimens profited from the CBSM training by a reduced epinephrine response under acute stress compared to the controls. In contrast, the CBSM patients under the influence of PI showed the highest ACTH reactivity in the TSST when compared to both the control group with PI-based regimens and the treatment group without PI-based regimens.

In consideration of an overall impact of PI on the autonomic nervous system and studies demonstrating the association of PI with elevated blood pressure (Crane et al., 2006; Palacios et al., 2006; Sattler et al., 2001; Seaberg et al., 2005) and increased aortic stiffness (Schillaci et al., 2005), it is interesting that we could not detect an influence of PI on the hemodynamic response to stress. Similarly to the epinephrine results, we found a CBSM treatment effect in pulse pressure, which was reduced in the treatment group compared to the control group when disregarding the influence of PI treatment.

Elevated pulse pressure is seen as risk factor for cardiovascular disease (Franklin et al., 1999; Haider et al., 2003) and a consequence of increased artery stiffness (Dart & Kingwell, 2001). Thus, the diminished pulse pressure in the CBSM group under acute stress might be a preventive factor, reducing the risk of cardiovascular disease.

As a third variable, which might account for our results, we consider the possibility of differences in the past medical history in our HIV-sample - although both groups were similar in important parameters of anamnesis (e.g. nadir of CD4 cells or number of CDC-C symptoms).

Variation in the kind of opportunistic infections during HIV course or differences in medication used in the pre-HAART era might affect endocrine parameters. Both factors were shown to produce endocrine aberration of the adrenal gland (Eledrisi & Verghese, 2001; Hofbauer & Heufelder, 1996). Furthermore, the HIV infection itself may lead to endocrine disturbances via its effects on the adrenal gland (Hofbauer & Heufelder, 1996).

Accordingly, patients might have autonomic dysfunctions, which appear in the early stage of the HIV infection (Freeman et al., 1990; M. Kumar et al., 1991) and which have been detected independently of any heart disease (Mittal et al., 2004). Opportunistic infections and direct and indirect effects of HIV were potentially etiologies for autonomic dysfunctions (Chen et al., 2002; Kan et al., 2000).

In consequence, many subclinical endocrine and autonomic deviations occur very early in the course of the HIV disease and might also reveal in the HAART-era. Thus, possible dysfunctions of the HPA axis and the SAMS might constitute an uncontrollable factor that impedes CBSM training-induced changes of endocrine and autonomic responses in an acute stress situation.

A final variable, which might account for our results, is the fact that the high variability in the actual course of HIV infection leads to a very heterogeneous sample. The side effects of HAART regimens differ between patients, depending on HAART combination. This provokes a high variability of disease progression among HIV-infected individuals. For example, some of the HAART treated patients developed metabolic distribution, others showed cardiovascular disease or gastrointestinal side effects.

The heterogeneity of the sample may further be strengthened by moderate exclusion criteria during screening. In our sample, equal distribution of actual disease was assured in both groups. Nevertheless, the extreme heterogeneity of HIV-infected patients in combination with a small sample size might have decreased the likelihood to find a CBSM treatment effect.

Several studies investigated the influence of CBSM training on base endocrine and autonomic outcome in HIV infected persons in the pre-HAART era. However, not all could detect that the CBSM training changed the observed stress parameters. In line with our results, Cruess (1999, 2000) did not find significant differences between the group assigned to the CBSM and the controls (Cruess et al., 1999; D. G. Cruess, M. H. Antoni, N. Schneiderman et al., 2000). Likewise, Mc Cain (2003) could not detect any differences in cortisol levels among CBSM participants (McCain et al., 2003). Although

Antoni (2000) found a significantly lower posttreatment level in norepinephrine in the CBSM group compared to the control group, alike us, he could not detect group differences of epinephrine at post-treatment levels (Antoni, Cruess, Cruess, Lutgendorf et al., 2000). Until now, Antoni's was the only study, which analysed sympathetic parameters after CBSM training.

Three studies could identify a reduction in cortisol levels in HIV-infected persons. But not all of them were methodologically comparable with our study. One study evaluated the effect of a bereavement support group on plasma cortisol (Goodkin et al., 1998). However the kind of techniques used in the CBSM training might be different from those used in bereavement support training. The second study focused on changes in pre-session salivary cortisol during relaxation training, which represents one part of the CBSM training (D. G. Cruess, M. H. Antoni, M. Kumar et al., 2000). Results in this study were based on only one saliva sample during the session. The third study analysed 24-hour urinary free cortisol levels after completion of the CBSM training (Antoni, Cruess, Cruess, Kumar et al., 2000).

In conclusion, the studies in the pre-HAART era do not find reliable evidence for the effects of the CBSM training on direct mediators of health outcome (e.g. endocrine parameters of the HPA axis and SAMS) in HIV disease.

5.4 Conclusion and outlook

To the best of our knowledge, this is the first study, which evaluates CBSM effects under a stress condition in samples recruited in the HAART-era.

In contrast to the pre-HAART era, the use of combinations of antiretroviral therapies has changed the course of HIV dramatically, resulting in a reduction of morbidity and mortality. However, HAART side effects become more prevalent in HIV infected persons and are still being discovered.

In consequence, the sample characteristics of acute illnesses are completely different than those of the pre-HAART era and the early history of HIV infection. Thus, it is not only difficult to compare physiological results in the HAART-era to studies carried out in the pre-HAART era, but rather, we conclude that it is impossible to transfer the pre-HAART results into the HAART era. Today it seems that treatment effects are hidden under the immense influence of HAART medication. Therefore, even if there were any biological effects of CBSM, it is unlikely to detect them in concurrence to HAART treatment effects.

Based on the fact that the impact of the CBSM training depends on antiretroviral treatment-regimens and considering the increasing adverse effects of HAART, further psychological intervention should focus on specific antiretroviral HAART regimens, respectively side effects. Homogeneity of the group sample might increase effectiveness of the intervention (Fitch et al., 2006).

In addition, one possibility to subtend the effect of HAART treatment is to increase the practise of stress reduction techniques over a longer period. Thus, patients with chronic diseases like HIV might need an accompanied therapy to profit from the training.

In general, measurements of indirect pathways (e.g. changes in health behaviour) may be more successful to examine the effect of the CBSM training than measurements of endocrine parameters, which were influenced by several confounding variables in HIV-infected patients.

Overall, our CBSM training might represent a good means to reduce the risk of cardiovascular disease in HIV infected populations under HAART. It should be established as a standard-of-care therapy offered to all HIV infected patients, especially those with cardiovascular side effect of HAART treatment.

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Curriculum vitae

Education

07/03-04/07	University of Zürich, Faculty of Arts, Institute of Psychology, Switzerland, **Ph.D. in Clinical Psychology** Supervisor: Prof. Dr. Ulrike Ehlert, Zürich Switzerland
10/96-04/03	University of Trier, Institute of Psychology, Germany, **Diploma in Clinical and experimental** Psychology (Master of science)
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Research Experience

06/04-04/07	International Ph.D. Program in Neuroscience, ETH & University of Zürich, Switzerland
10/01-05/02	Master thesis, University of Trier (Supervisor: Prof. Dr. Dirk Hellhammer) "Magnetic resonance imaging of adrenal gland volume and functional reactivity of the adrenal gland in fibromyalgia syndrome (FMS), posttraumatic stress disorder (PTSD) and chronic pelvic pain (CPP)"
05/01-09/01	Internship, McConnell Brain Imaging Center, Neurological Institute and Hospital, Montreal, Canada
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10/00-02/01	Internship, University of Heidelberg, Psychiatric Hospital, Department of Child and Adolescent Psychiatry
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